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DISEASES
of the
NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

XX **Supplement**

AUGUST
1959

NIALAMIDE:
A New Psychotherapeutic Agent

REPORTS OF PAPERS

READ AT

A SCIENTIFIC MEETING

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Introductory Remarks

DAVID J. IMPASTATO, M.D.

Today we are about to take a good look at various phases of knowledge on nialamide. All research in medicine is designed to benefit the patient. The practitioner, who ultimately dispenses the agent, is an integral part of the process. Without him, medical research would be pure research and not applied research, as it is intended to be.

The essayists here in congress, who have carefully and painstakingly assembled this knowledge, are the most prominent and erudite in their field and we are all very grateful for their help and philanthropy.

The Eastern Psychiatric Research Association, officially incorporated four years ago, has a membership of nearly 200. This membership, among whom we are proud to say is the President of the American Psychiatric Association, Dr. William Malamud, is made up mainly of practicing and research psychiatrists. The chief aim of the Eastern Psychiatric Research Association is the fostering of clinical studies on therapeutic methods, drugs and apparatus in psychiatry; and the presentation and publication thereof. Clinical study is here used in its broadest sense and includes not only the study of the effect of an agent on the patient's clinical condition but also chemical, pharmacologic and cognate investigations, all leading to a sound understanding of the agent, its indications and clinical effects, its chief site of action, its absorption, fate and excretion and its side actions.

At the recent meeting of the American Psychiatric Association in Philadelphia, a round table discussion entitled "Integration of Somatic Therapies in Psychiatry" I had occasion to say a few words on electroshock therapy (ECT) and drugs. I had special reference to depressed patients, electroconvulsive therapy and psychic energizers. I do not have to inform this audience of the extremely favorable clinical reports on these drugs by many of the original investigators; and of the expressed opinion of some that at last, after 20 years, they see the end of ECT. Some of these clinicians have practically abandoned ECT in favor of the psychic energizers. Is this wholesale shift of therapeutic agents justified? Many of us will answer in the affirmative. But are we sure of our answer? No one will dispute, that today the most efficient and reliable therapeutic agent available for relief of depression is ECT. This modality is far more effective than any drug presently available. Its results are quick and long lasting. This cannot be said of the psychic energizers we have been using. They yield results slowly, the number benefited is considerably less than with ECT and to prevent relapse the drug has to be given for months upon months.

Since the advent of succinylcholine a few years ago ECT has become the safest treatment in psychiatry. With psychic energizers we always have the threat of liver damage and possibly death. To guard against this, we subject the patient to repeated blood counts, urine and liver studies. The long duration of the treatment and the repetition of these tests make the treatment more costly than ECT. More important than the cost, is the fact that the patients are not relieved quickly and are subjected to a longer period of suffering.

The originator of ECT, Dr. Ugo Cerletti, who was recently in this country, expressed the opinion that ECT was a trying treatment and that since its inception he had been attempting to find a substitute. As you all know he has experimented with injections of emulsions of shocked pigs brains. His results have been encouraging but not conclusive. We all have, for a long time, wished that some day we may have an injection or a drug which will give comparable results to ECT in both percentage of cures and rapidity and duration of improvement. Until such a drug becomes available let us not delude ourselves by being over enthusiastic about any agent less effective than ECT. Let us not become second rate therapists: second rate because we are afraid to use an agent known definitely to be superior and substitute in its stead a second best agent. We do hope that nialamide, now to be discussed, will prove to be the agent which we are looking for. Should this not be so, let us hope that these studies will lead us to discover specific indications for its use at least in certain patients. We must be careful and conservative in passing judgment on any therapeutic agent: for undeserved overenthusiasm may guillotine any beneficial effect it may have.

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DISEASES *of the* Nervous System

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Nialamide is the generic name for the compound made available by Pfizer Laboratories, Chas. Pfizer & Co., Inc., under the trade name of "Niamid."

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A Pharmacologic Summary of Nialamide

ROBERT P. ROWE, PH.D.

The subject of this symposium is nialamide,* an agent which was developed as an antidepressant of low toxicity. Figure 1 shows the structure, in which the similarities and differences of nialamide compared to other monoamine oxidase inhibitors can be seen.

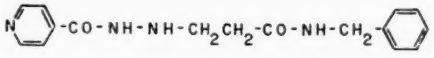

Figure 1.

The substituted isonicotinic acid hydrazide is similar to iproniazid. However, a benzylcarboxamido configuration added to the alkyl chain has endowed this molecule with some unique pharmacological properties, which may, in part, explain the interesting results from studies of its metabolic fate. This important phase of the pharmacological study of nialamide is reported in Dr. Bloom's paper which follows. From the point of view of its laboratory studies and clinical use, nialamide is in a fairly advanced stage of development at this time. However, as with any compound of pharmacological or clinical significance, much more work will be done. In this paper, the development of nialamide is retraced as a means of pointing out some of its pharmacological characteristics.

In principle, the discovery and development of a new drug takes place in three phases:

1. Recognition of a potentially useful biological effect in a chemical compound;
2. Determination of the relative safety factor in animals;
3. Establishment of activity, therapeutic usefulness and safety in humans.

In the present case, due to the substantial accumulation of literature on iproniazid, several types of chemical structure were known to be associated with the activity desired. Therefore, a structural starting point was available. However, the development of iproniazid as an antidepressant was based on clinical observations rather than laboratory studies. Therefore, there was need to develop a laboratory test for antidepressant action which was practical and sufficiently precise to show statistically significant differences in potency between compounds being tested. This is a major problem when little, if any, information is available concerning the etiology of the disease process in man. This is particularly true in the case of mental disease where even our understanding of the physiology and biochemistry of normal brain function is so rudimentary.

To aid in designing a test procedure, use was made of the report that reserpine and iproniazid, in general, had opposite effects on psychiatric patients, that is, the patient whose condition was improved by one agent was generally made worse by the other. This, coupled with the biochemical studies which showed opposite effects on brain stem amines due to these two agents, suggested a possible basic relationship between the action of reserpine and the disease process of endogenous depression. With this information, it was believed that a laboratory test could be devised which would be a rational approximation to the clinical disorder. Specifically, a reserpine induced depression was used as the model.

Besendorf and Pletscher[1] reported that animals treated with iproniazid were temporarily protected against reserpine induced depression. A modification of this concept, referred to as "reserpine antagonism,"[2,3] was used to test compounds for their pharmacodynamic characteristics as antidepressants. By this test, it was found that the reserpine antagonist potency of nialamide varied from one species to another but was always equal to or greater than that of iproniazid.

Potency of nialamide relative to iproniazid is shown in Table 1.

Figure 2 illustrates the reserpine antagonist action of nialamide in cats.[4]

Iproniazid was known to block monoamine oxidase *in vitro* and *in vivo*. This was felt to

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From Macrobiology Department, Pfizer Therapeutic Institute, Maywood, N. J.

*Trade name Niamid, Chas. Pfizer & Co., Inc.

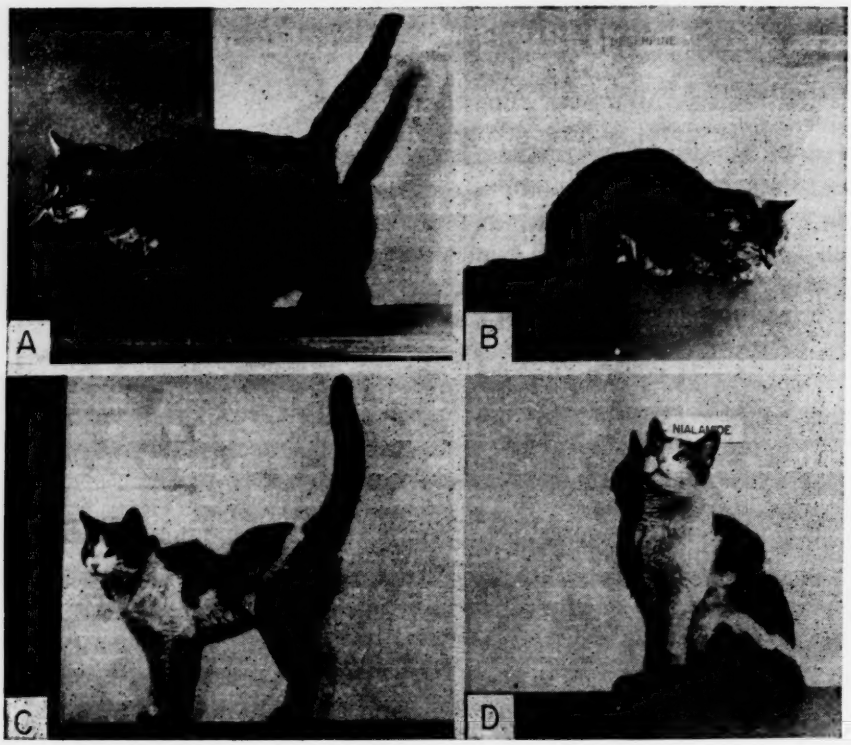

Figure 2.

A. Cat, untreated.
C. Cat, 24 hours after nialamide, 5 mg./Kg., PO.
Cats in A and C received reserpine, 1 mg./Kg., IV, immediately after pictures were taken.
B & D. Two hours after reserpine injection.

TABLE 1

Reserpine Antagonist Potency of Nialamide*

Mouse	10X
Rat	1X
Guinea Pig	1—1½X
Cat	10—12X
Dog	3X

*Potency relative to iproniazid.

TABLE 2

*In Vitro Inhibition by Nialamide of Rabbit Brain Monoamine Oxidase**

Nialamide moles/liter	5 HT Metabolized micro gm/30 min.	Percent Inhibition
1×10^{-3}	0	100
5×10^{-4}	0	100
1×10^{-4}	2	94
5×10^{-5}	14	56
1×10^{-5}	29	10
Control	32	—

*K. F. Finger, Nat'l. Inst. of Health.

be a necessary condition for antidepressant activity. Consequently, nialamide was tested for MAO inhibitory activity *in vitro,* using rabbit brain homogenate and was found to give 50% bloc at 5×10^{-5} moles/liter (Table 2). This and the following *in vitro* studies were performed by Dr. K. F. Finger of the National Institutes of Health.[2,3]

In vivo activity was checked by two techniques[2,3]: by indirect measure of MAO inhibition using potentiation of the pyretic effect of 5-hydroxytryptophan in rabbits and by direct measure of MAO activity and serotonin content of brain stem tissue from nialamide treated dogs. Both of these methods demonstrated that nialamide was a potent MAO inhibitor, and permitted a quantitative comparison with iproniazid. Nialamide had 2.5 times the potency of iproniazid in the rabbit and three in the dog. An interesting fact appeared as a result of the determination of brain stem amine content in the treated dogs. Whereas nialamide, iproniazid and JB-516 all caused an increase in brain stem serotonin, only nialamide caused a concomitant increase in norepinephrine levels.

At the time that this observation was made, only differences in the character of the reserpine antagonist response of dogs to nialamide and iproniazid had been noted. Since then, several other outstanding differences have come to light, such as the lack of toxic effect on the liver, the absence of a postural hypotensive effect,[5,6] and the lack of a blocking action on the perfused superior cervical ganglion.[7] Whether these separate observations have a factor in common is at present an unanswered question, as is the significance of the effect on brain stem norepinephrine.

Having established the antidepressant activity of nialamide by our criterion and its MAO inhibitor potency, it was next necessary to investigate the relative effectiveness of the oral as compared to the parenteral route. As had been suspected during the earlier studies, and proven by tests, nialamide was as effective orally as intraperitoneally. This was considered advantageous

since the oral route is the one of choice where an agent is to be given on a repeated dose regime.

The last two pharmacodynamic characteristics considered during preliminary studies with nialamide were the rate of onset and duration of action. Using tests for the degree of protection against reserpine induced depression, nialamide was found to have a substantially faster onset but no greater duration of action than iproniazid (Table 3). The maximal level of activity was reached in about one and a half hours for nialamide compared to four or five hours for iproniazid. They both showed a slow decline in activity over a two week period following a single oral dose.[2,3]

The pharmacological properties of a compound must be considered against the background of its toxicity. A simple procedure was devised to give an indication of potential hepatotoxic action in new compounds. This was the prolongation of hexobarbital anesthesia, because the rapid termination of the anesthetic action is dependent upon active metabolic degradation by the liver. Interference with liver function prolongs the anesthetic effect. A variety of known hepatotoxic agents, such as carbon tetrachloride, have been shown to prolong hexobarbital anesthesia. Applying this test, nialamide was found to have very little potentiating action compared to iproniazid,[2,3] a fact which was interpreted as suggesting low hepatotoxic action. Therefore, it was recommended for toxicological evaluation. Dr. C. S. Delahunt, who carried out this study,[8,9] was faced with the problem of devising a method for early appraisal of liver damage. Many species and routes of administration were tried before selecting the oral route in dogs as the one of choice. The livers from dogs given 60 mg./Kg. of nialamide daily for 14 days showed no gross or microscopic changes. With these favorable results, a chronic toxicity or tolerance study was started. For this, the rat and dog were used.

Weanling rats of both sexes were fed diets containing from three to 300 mg. of nialamide per Kg. of body weight. Mortality, food consumption, growth rate, blood and tissue changes were recorded. The results are summarized in Table 4.

TABLE 3

Rate of Onset of Action

Time[1] Hours	*Percent Antagonism*[2] Nialamide 8 mg./Kg., P.O.	Iproniazid 100 mg./Kg., P.O.
1/3	33	—
2/3	40	—
1	—	24
1 1/3	56	—
2	67	38
3	65	56
4	67	64
5	63	67

Duration

Days	*Percent Protection*[3] Nialamide 10 mg./Kg., I.P.	Iproniazid 100 mg./Kg., I.P.
1	95	81
2	98	83
4	95	75
7	81	60
9	77	57
11	72	54

1. Time interval from administration of MAO inhibitor to administration of reserpine, 5 mg./Kg., I.P.
2. Antagonism of ptosis induced by reserpine.
3. Duration of protection against facilitation by reserpine of Metrazol induced convulsions.

TABLE 4

Parameters Employed in Six Month Chronic Rat Toxicity Study of Nialamide at Doses up to 300 mg./Kg.

1. Mortality	Insignificant effect
2. Food consumption	Insignificant effect
3. Growth rate	Retardation
4. Hematology	No effect
5. Pathology	No effect

Some mortality occurred in males at 300 mg./Kg. Food consumption was essentially unaffected. Growth rate was normal up to the 30 mg./Kg. level where some retardation occurred; this effect increased with dose to a severe depression at the 300 mg./Kg. level. At the end of the 6, 12 and 26 week periods, blood samples were taken and some of the animals were sacrificed for autopsy. Hemoglobin content, red, white and differential white cell counts were determined and 15 tissues were taken for microscopic examination. These were all found to be within normal limits. The study is being continued with the remaining rats for at least a year. The gross anatomical and histological evaluation of the tissues from the chronic studies was

done by Dr. R. B. Stebbins of our laboratories.

A six month canine oral tolerance study with 30 mongrel dogs has been completed. Nialamide was given in the range of 3 to 60 mg./Kg. six days of the week. The dogs were observed for symptoms daily and weighed weekly. At the start and after 2, 4, 12 and 26 weeks, blood studies were done for blood urea nitrogen, fasting blood sugar, bromsulphalein retention (30 minutes), alkaline phosphatase, serum transaminase, hemoglobin content, red, white and differential white cell count. There were no toxic symptoms; all animals maintained or increased body weight. All the above measurements were within normal limits up to the 60 mg./Kg. level where a mild reduction in hemoglobin content (Figure 3) and red cell count occurred. Animals were sacrificed at intervals during the study and 20 or more tissues examined microscopically. There were no abnormalities, gross or microscopic, in the tissues from dogs on test for as long as six months.

A similar study was started in beagles at 70, 80, 90 and 100 mg. of nialamide per Kg. of body weight and will be continued for one year. These high doses cause a bufotenin-like syndrome,[10,11] an increase in body temperature, heart rate and respiratory rate. The 100 mg./Kg. dose was lethal to all animals in an average of seven days. The 70, 80 and 90 mg./Kg. doses were lethal to about half the animals in 14 days. The survivors showed, at the end of a month, a slight elevation in blood urea nitrogen and alkaline phosphatase, and a decrease in hemoglobin content and red cell count. Moribund animals were sacrified and necropsied. Tissues examined were free of abnormalities due to nialamide.

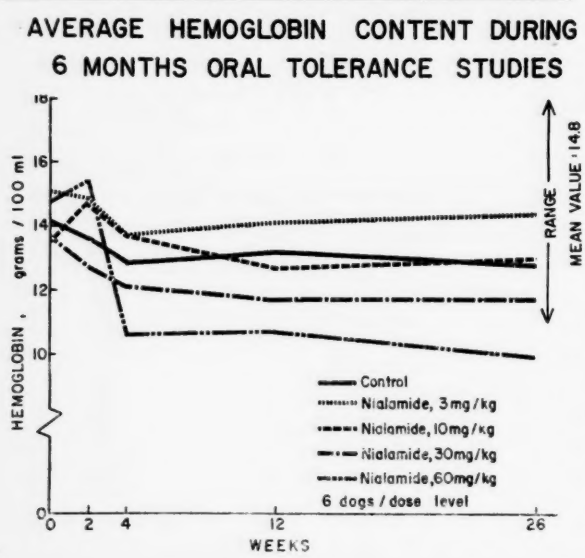

Figure 3. Normal Values of blood hemoglobin in the dog: 14.8 (11.0-18.0) gm/100 ml. blood. Ref. p. 175, "Handbook of Biological Data," W. S. Spector, editor. W. B. Saunders Company, 1956.

A six month study in Rhesus monkeys was done, using nine test and three control animals. Nialamide was given orally six days a week at 10, 25 and 50 mg./Kg. Laboratory determinations similar to those on the dogs were carried out. Biochemical, hematological and histological findings were essentially normal except for a slight reduction in hemoglobin content and red cell count at the highest dose.

The next property of interest from a clinical point of view, after the antidepressant activity and toxicity of a compound of this type, concerns the effect on the cardiovascular system. The cardiovascular pharmacology studies on nialamide have been done by Dr. Finkelstein of our laboratories.[12]

Although the intravenous administration of nialamide would rarely be used clinically, it constitutes an important parameter of a pharmacological study. Intravenous administration of doses up to 100 mg./Kg. to anesthetized dogs and cats caused an acute, moderate, transient fall in blood pressure, the magnitude and duration of which were dependent upon dose and rate of administration. The effect appeared to be primarily due to a direct action on peripheral vascular tissue. At the higher doses, heart rate was also decreased. Nialamide, given orally to normotensive dogs in doses of 5 and 30 mg./Kg. twice a day for 50 or more days, caused no significant changes in blood pressure or heart rate.

Because of the occurrence of postural hypotension with iproniazid and other monoamine oxidase inhibitors, a test was used to assess the integrity of the compensatory mechanism which usually prevents this. An experimental design was used in which blood pressure was measured while the dog was tilted from a horizontal to a vertical position. In this test, anesthetized dogs which

had received 60 mg./Kg./day of nialamide orally for seven days or up to 100 mg./Kg. I.V. showed no postural hypotensive effect. By contrast, JB-516, 10 mg./Kg. orally or 5 mg./Kg. I.V., regularly produced a prompt orthostatic hypotension under these conditions. On the other hand, 5 mg./Kg./day of iproniazid orally for seven days, or up to 100 mg./Kg. I.V., has not consistently shown such an effect. Although it appears that laboratory studies are not yet able to distinguish between those agents which will cause postural hypotension in patients and those which will not, they have not contradicted the clinically observed absence of such an effect for nialamide.

Other pharmacological properties of nialamide have been studied, a few of which will be briefly summarized here. Effects on conditioned behavior in well-trained rats on several schedules have been studied by Dr. A. Weissman of our laboratories. On a program in which rats lever pressed, sometimes for food, and other times to avoid shock, little effect was seen up to 100 mg./Kg., I.P. At that high dose, 22 and sometimes 46 hours after injection, lever pressing for food was largely eliminated, with little effect on the shock avoidance component. On several schedules examined in which rats were required to lever press at prescribed rates for food, little effect was seen up to about 100 mg./Kg., where rate reductions tended to set in. On a few programs, however, in which very low but sustained rates of lever pressing were called for, some rats increased their rates in doses of 30 mg./Kg., I.P., 22 hours after injection.

Studies on the protective effect of nialamide against electroshock-induced convulsions have been carried out by Dr. B. Korol of our laboratories. A significant degree of protection is obtained at 100 mg./Kg. in the mouse, four hours after administration. Some degree of potentiation of the protective action of phenobarbital is obtained at 10 mg./Kg.

Other studies include demonstration of potentiation of the anesthetic action of pentobarbital in the same way but to a lesser extent than of hexobarbital, and lack of potentiating effects on barbital, ethchlorvynol, ethanol, ouabain, Demerol, or aspirin. Of the analgesics, only morphine showed any potentiation and here only to a slight degree. A measure of effect on food intake in rats at 5 and 30 mg./Kg. showed no effect compared to racemic Amphetamine hydrochloride at 6 mg./Kg. which caused a 50-75% depression sustained over a five hour period.

Summary

Nialamide has been found to be a potent, specific, relatively non-toxic antidepressant with important features from a clinical point of view, that is, no adverse effect on liver function or postural hypotensive activity.

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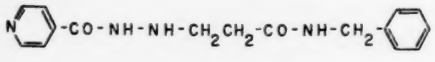
Metabolism Studies with Nialamide

(A Preliminary Report)

BARRY M. BLOOM, PH.D., RICHARD L. WAGNER, JR., PH.D., CHARLES S. DELAHUNT, D.V.M., and ERIC C. SCHREIBER, M.S.

Toxicological studies with nialamide* in dogs and other species have been characterized by an absence of hepatic injury or other tissue pathology in the test animals following chronic administration of daily doses as high as 60 mg./kg. over a six month period.[1] Being conditioned to numerous research reports dealing with liver damage caused in animals by hydrazine and its derivatives,[2,3] we were prompted by this finding to ascertain whether the freedom from toxicity noted with nialamide results from a pathway of metabolic breakdown divergent from that observed with previously studied hydrazine derivatives.



Nialamide
1-[2-(Benzylcarbamyl)ethyl]-2-isonicotinoyl-hydrazine

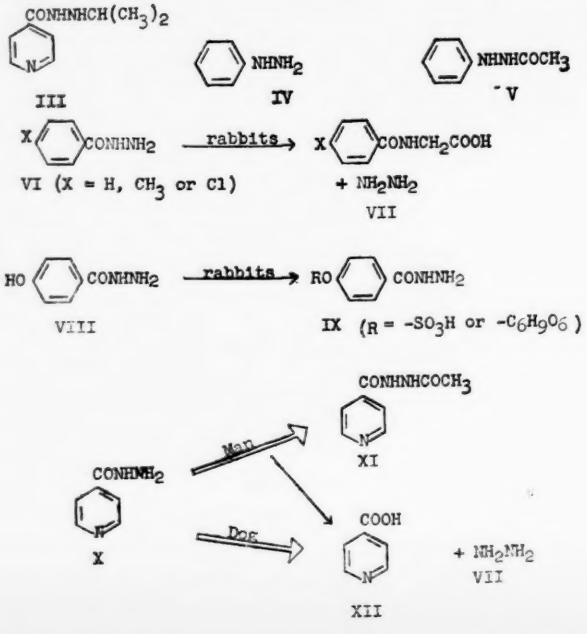
It must be stated at the outset that the findings in this report stem largely from scouting experiments and are preliminary in nature. As we continue *in vivo* studies with hydrazine-derived monoamine oxidase inhibitors, our experimental designs will inevitably benefit from the experience of these early studies, and it is highly probable that at least some of the quantitative data in this note will be extended before appearing in the literature in final form. Nevertheless, certain of these first experimental findings reveal such clean-cut differences in comparative metabolism as to justify this communication.

As our working hypothesis we chose the argument previously put forth, at least in part, by others[4] that acylated hydrazines or *hydrazides* (I) are seldom intrinsically toxic in high degree, but that the free *hydrazines* (II) derived from them very frequently cause damage to blood and tissue constituents. Thus it seems likely as Ranserved in animals after the administration of certain hydrazide-type drugs such as iproniazid (Marsilid, 1-isonicotinoyl-2-isopropylhydrazine) (III)[1,6] result from the biochemical actions of a free hydrazine moiety liberated *in vivo* from the parent drug by a metabolic cleavage process.

$$\underset{\text{I}}{\text{RCONHNHR'}} \xrightarrow{H_2O} \text{RCOOH} + \underset{\text{II}}{\text{NH}_2\text{NHR'}}$$

(R' = hydrogen, alkyl or aryl.)

Strong support for this contention can be derived from published data on the toxicology and metabolism of a variety of hydrazine compounds. For example, one of the first well-designed studies on the toxicity of hydrazine derivatives carried out by Bodansky[7] in 1924 showed in dogs that a single dose of phenylhydrazine hydrochloride (IV) (25.4 mg./kg. s.c.) caused a deficiency in liver function within 12 days. Fatty changes in the liver were observed at autopsy. In marked contrast, a simple hydrazide deriva-



From Research Division, Chas. Pfizer and Co., Inc., Brooklyn, N. Y.

*Niamid is the registered tradename of Chas. Pfizer and Co., Inc., for nialamide.

tive of IV, acetylphenylhydrazine (V), did not measurably disturb liver function even dall[5] has inferred that the toxicities ob- at a much higher dose (67.6 mg./kg. s.c.). Autopsy after nine days revealed very little hepatocellular damage caused by the acetylated compound.

An intensive study[4] by Williams and his colleagues also serves to confirm the hypothesis just stated. Following the observation that benzhydrazide (VI, X=H) as well as its *p*-methyl (VI, X=CH_3) and *p*-chloro (VI, X=Cl) analogs were quite toxic to rabbits, urinary excretion studies revealed that metabolic cleavage had occurred with all of these compounds resulting in the liberation of substantial quantities of free hydrazine (VII) *in vivo*. Very different results were obtained with the relatively non-toxic *p*-hydroxybenzhydrazide (VIII). In this case glucuronide (IX, R=—$C_6H_9O_6$) and sulfate (IX, R = —SO_3H) formation proved to be the predominant metabolic conversions. None of the alternative cleavage products indicative of hydrazine liberation could be detected. To more or less clinch the argument *m*-hydroxybenzydrazide proved to be intermediate in toxicity between benzhydrazide and its *p*-hydroxy-derivative. Urinary studies with this *m*-hydroxy compound showed that glucuronide and sulfate formation as well as cleavage had occurred, resulting in *partial* liberation of free hydrazine. Thus in a relatively small group of closely related hydrazine derivatives we find a striking correlation between toxicity and the amount of free hydrazine liberated during drug metabolism.

Perhaps more germane to the discussion at hand are laboratory findings with the familiar anti-tubercular agent, isonicotinic acid hydrazide (X), whose widespread use has yielded dependable statistics regarding the clinical incidence of typical hydrazine toxicities. Merritt and Fetter[8] have recently pointed out that the entire medical literature written in English, records only four cases of jaundice and one fatal hepatitis attributed to the use of this drug. Such a low incidence of hepatotoxicity might seem surprising, especially considering the large doses often administered clinically in the course of therapy with this hydrazine derivative, but again metabolism studies in man have provided a thoroughly satisfactory explanation for this apparent anomaly. Hughes[9] has shown that in contrast to the dog where cleavage to free hydrazine *does* occur (and, incidentally, where gross liver pathology *is* observed) man metabolizes isonicotinic acid hydrazide predominantly by acetylation thereby sparing his system from exposure to free hydrazine.

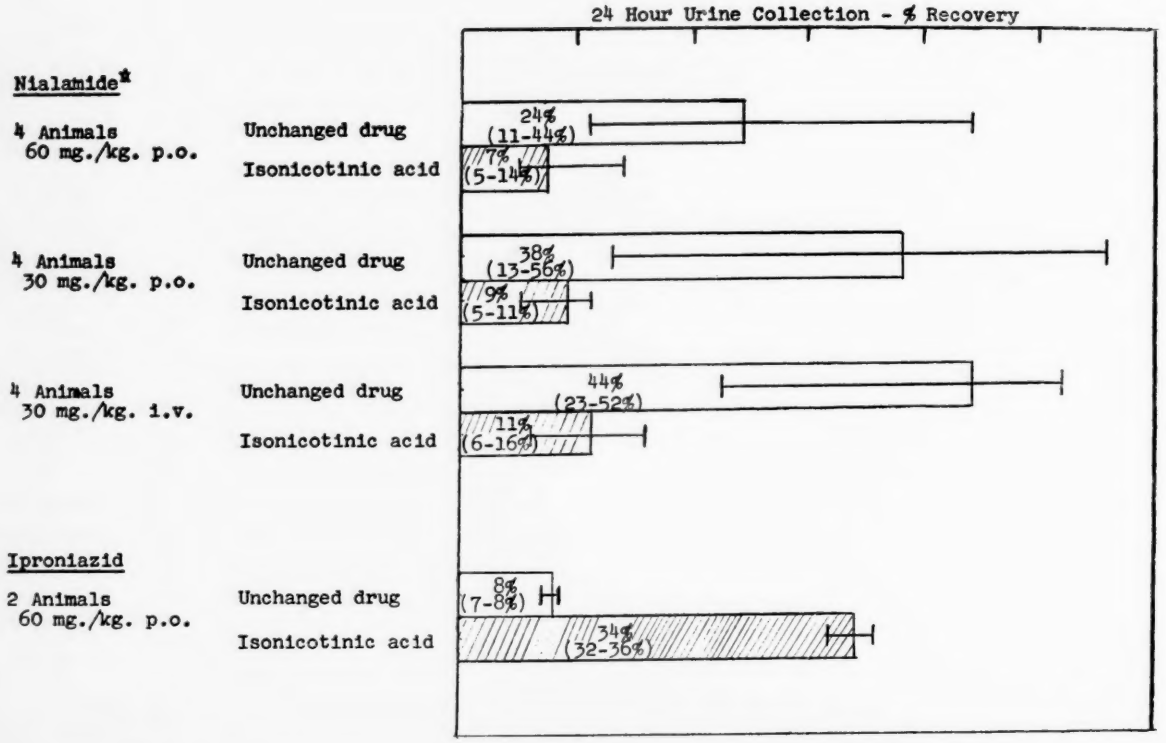
Although these arguments based on metabolism studies are not intended to equate the clinical situation in any specific way with pathology induced in animals by hydrazine derivatives, it is impressive to note that even in man it has been possible to correlate[10] the occurrence of a certain type of toxicity, peripheral neuritis, presumably due to chemical interaction between pyridoxal and isonicotinic acid hydrazide (X), with the variable capacity of patients to detoxicate the hydrazide in normal fashion, that is, by acetylation.

Convinced by literature reports of this sort that metabolic factors very often underly the presence (or absence) of toxicity with hydrazine derivatives, we undertook to compare the metabolism of two anti-depressive hydrazides, nialamide and iproniazid, chosen primarily because of the dramatic toxicological differences observed between them in the dog. In particular, we were anxious to quantitate the degree to which these drugs were cleaved to a hydrazine fraction both in dog and man. For this purpose we utilized the indirect method of measuring urinary excretion of isonicotinic acid. This was necessitated by the insurmountable technical difficulties that would have been involved in measuring the highly reactive, and therefore elusive, hydrazine fragment itself. Dogs were given substantial single doses of the two test compounds and urine samples were collected over a 24 hour period. The results are summarized in Figure 1.

The most striking finding in dogs is the low isonicotinic acid (XII) excretion following nialamide in contrast to the situation with iproniazid where more than one-third of the ingested dose can be accounted for as XII. The data also indicate that substantial

Figure 1

URINARY EXCRETION PATTERN IN DOGS



* Both nialamide and INA were absent in all 48 hour urines.

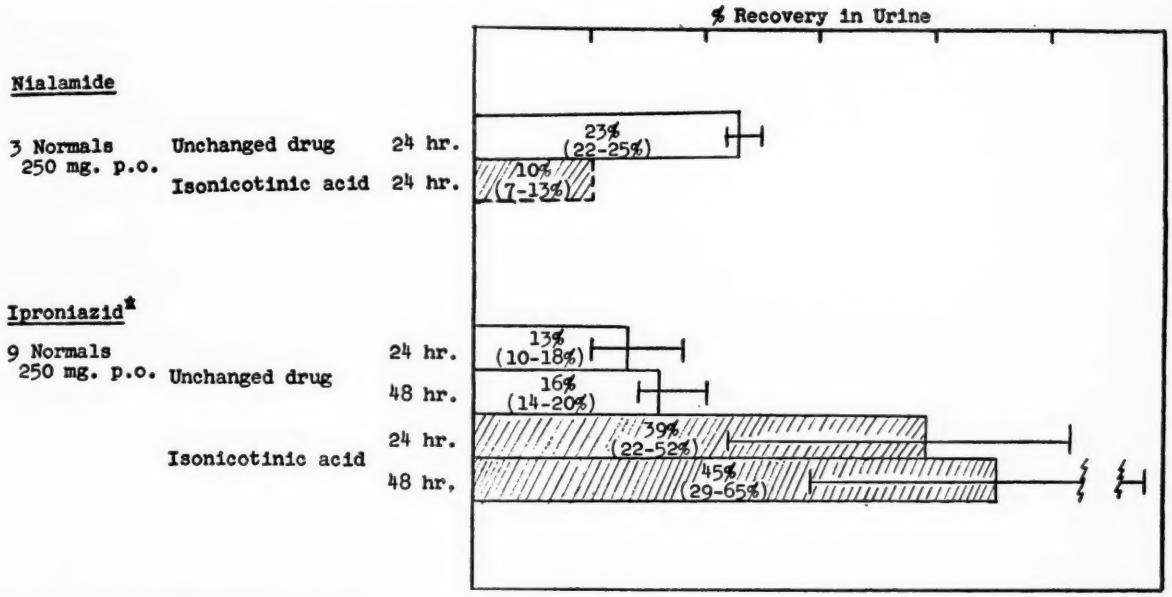
quantities of unchanged nialamide are rapidly excreted by this species, whereas very little iproniazid is recovered in unchanged form. The urine from nialamide-treated animals collected during the second day (24-48 hours post drug administration) invariably failed to contain measurable amounts of unchanged drug or isonicotinic acid. If one accepts the reasonable assumption that indiscriminate liberation of hydrazine fragment from these compounds *in vivo* is undesirable from a toxicological point of view, it follows that the metabolic factor uncovered in this investigation probably underlies the pronounced difference in canine tolerance for these two structurally-related drugs.

We are currently attempting a similar evaluation of *human* urinary excretion patterns following single dose nialamide (250 mg. p.o.).[11] Our preliminary findings are shown in Figure 2 along with directly comparable literature data for iproniazid. As in the dog we find a rather substantial recovery of unchanged nialamide in the 24-hour urine samples along with low levels of isonicotinic acid. The isonicotinic acid levels in human urines after nialamide are in fact so low (in relation to blank values for control urines) that we do not yet feel justified in assigning them a definite quantitative value. This is indicated by the dotted lines in the bar graph. These observations differ greatly from the findings of DeRitter and co-workers[12] following iproniazid administration to normals (also at the 250 mg. p.o. dosage level) when urine samples revealed isonicotinic acid equivalent to almost half of the ingested dose of drug.

The synthesis of nialamide specifically labelled with carbon-14 in the benzylic position (the carbon atom adjacent to the benzene ring) has been completed. Current studies in dogs with this material are directed toward the determination of plasma and tissue levels as well as excretion patterns. Two unidentified urinary metabolites which are formed in significant amount (not nialamide or isonicotinic acid are discernible in chromatograms of radioactive urine samples. Radioactivity is also detectable in the

Figure 2

URINARY EXCRETION PATTERN IN HUMANS



* All iproniazid data taken from reference 12.

bile following nialamide administration. Peak plasma levels following oral administration (30 mg./kg.) occur rapidly (30-180 minutes), drop to a low level by 8 hours and are essentially zero at 24 hours. This pattern of rapid drug absorption and prompt disappearance from plasma following oral administration strongly resembles that observed earlier with iproniazid and isonicotinic acid hydrazide.[13,14]

In contrast to the other hydrazine-derived antidepressive agents of current clinical interest where substituents in the hydrazine moiety are invariably hydrocarbon in character, nialamide is functionally substituted with a carboxamido grouping in that critical sector of the molecule. Besides ascribing certain unique pharmacological actions[15] to such a structural characteristic, it is also tempting to hypothesize a route of metabolism which involves the amide grouping, especially since the findings related above show that direct cleavage to isonicotinic acid is not a predominant pathway of metabolism for nialamide in the dog and normal man. Studies currently underway in our laboratories will attempt to shed further light on this and related problems.

Methods

Colarusso and co-workers[16] reported that iproniazid yields a color with an acidic solution of ammonium molybdate that can be used for analytical purposes. The method utilized for the determination of nialamide in dog urine is based on the color forming properties of this compound with the ammonium molybdate reagent. Nialamide is isolated from dog urine by a two-stage extraction procedure which includes: (1) extraction of urine, buffered at pH 6, with sec-amyl alcohol in the presence of sodium chloride, and (2) washing of the sec-amyl alcohol phase with water. The sec-amyl alcohol phase from the second extraction is treated with the ammonium molybdate reagent in acetone solution; the nialamide content is determined by measurement of the absorbance at 439 mu and 543 mu. The recovery of nialamide from urine samples, to which known amounts (50 to 600 micrograms/ml.) of the drug were added, is approximately 85%. The blank values on urine specimens (free of nialamide) processed through the above assay procedure are reasonably small and reproducible; apparent nialamide concentrations of 7 micrograms/ml. are indi-

cated. The technique of Brodie and Udenfriend[17] for evaluating the specificity of an assay procedure was applied to this method for nialamide and the results indicate that there is no serious interference from metabolites. Iproniazid was determined in a similar fashion.

The method used for the determination of isonicotinic acid in dog urine is that described by Hess and collaborators.[14]

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DISCUSSIONS

Urinary Tryptamine in Hypertensive Patients Treated With JB-516 and Nialamide

SIDNEY UDENFRIEND, PH.D.

As a discussant I am supposed to remark on the previous papers. However, I have also been assigned the job of presenting some work going on in the National Heart Institute. Because of the limitation of time I shall use some of the free time later on for the discussion of the previous papers and present our data first. Actually it bears on what was said by the previous speakers because we too would like to obtain chemical or laboratory correlates to the human studies with the monoamine oxidase (MAO) inhibitors. I was glad to see that the previous speaker brought the human animal into the discussion a number of times.

In the Heart Institute, Dr. Albert Sjoerdsma, Dr. Louis Gillespie, and their colleagues have been interested in drugs that can influence blood pressure. They were interested to find that there was a relationship between the central and cardiovascular actions of the MAO inhibitors. I would like to point out that to the biochemist the MAO inhibitors have proven to be a wonderful group of compounds because they have uncovered many routes of metabolism that have heretofore not been observed. In administering the MAO inhibitors to patients or animals examination of the urine reveals a huge number of amines, some have been identified, many still remain to be identified. All of them are derived from a parent amino acid by decarboxylation. Thus, if one administers tryptophan or tryptophan plus iproniazid to guinea pigs, one finds appreciable amounts of the corresponding amine, tryptamine, in liver and brain. One also finds a relatively large increase in the urinary excretion of tryptamine which parallels the elevations in tissue levels.

Tryptamine is merely one of the amines which is increased in tissues and in urine following administration of MAO inhibitors. Tyramine, ortho-tyramine, meta-tyramine, and phenylethylamine are a few of the other compounds whose concentrations in urine are increased following treatment with MAO inhibitors. Trying to relate the effects on blood pressure to the biochemical action of the different MAO inhibitors, Dr. Sjoerdsma and our group thought it would be wise to try to devise a means of arriving at common dosages from drug to drug; that is, dosages which would possibly produce similar degrees of MAO inhibition in patients. The idea of measuring the level of amine excretion in urine as an index of MAO inhibition was considered and tested. Although the increases may not be exactly proportional to the effects of the MAO inhibitors in every tissue, the method is simple and is the nearest thing to a chemical test reflecting therapeutic activity that is now available.

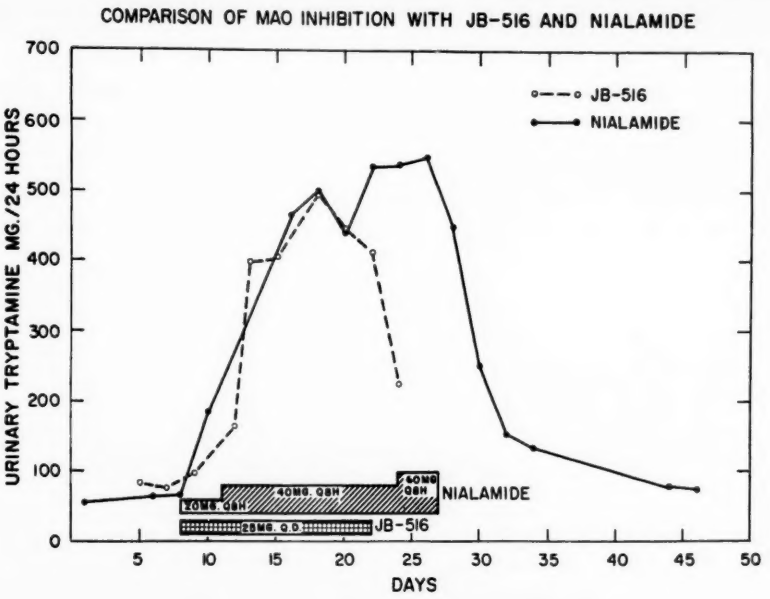

Figure 1. **Effects of JB-516 and Nialamide on Urinary Tryptamine (A. Sjoerdsma and L. Gillespie, unpublished data).**

In Figure 1 are shown variations in the excretion of tryptamine in urine following therapy with two MAO inhibitors. The patient, after a control period, was placed on JB-516. He was then permitted to return to control levels, following which he was given nialamid (the dosages are presented in the figure). It is apparent that with the two compounds one can obtain marked increases in urinary tryptamine; over ten fold increases have been observed in various patients. It is also obvious that one can indeed arrive at dosages for each of the drugs which produce comparable excretions of tryptamine. I should like to point out that both compounds are long lasting and that in each case it takes many days for the tryptamine values to return to normal.

Since there had been reports of a lack of effect on blood pressure of nialamid, and a definite effect with JB-516, Dr. Sjoerdsma wanted to compare these two compounds as anti-hypertensive agents at equivalent dosages, and also to find out what dosages were needed to arrive at equivalent effects on MAO. The results which were obtained (Table 1) indicate that with respect to its effect on blood pressure nialamide at comparable dosage to JB-516 is completely inactive. What is interesting is that these conclusions can be derived from a study on a limited number of patients. When JB-516 is given at 25 mg/day one gets near maximal effects on urinary tryptamine, with 50 mg/day there is only a slightly greater excretion. We don't know whether this represents almost complete MAO inhibition in man. It would be interesting, in fact, to determine the degree of MAO inhibition in man on biopsy or autopsy material.

We feel that the same type of information might

TABLE 1

MAO Inhibition with JB-516 and Nialamide

Effects of JB-516 and Nialamide on Blood Pressure and Urinary Tryptamine (A. Sjoerdsma and L. Gillespie, unpublished data).

Patient	Drug	Dose mg/day	Range of Daily Urinary Tryptamine Excretion, mg/24 hrs	Standing Blood Pressure, mm.
A.F.	——	—	54- 81	130/80
	JB-516	25	415-498	100/60
	Nialamide	60	180-200	—
	Nialamide	120	441-540	130/84
	Nialamide	180	550	—
G.S.	——	—	89-101	160/125
	JB-516	25	555-616	120/90
	Nialamide	120	147-216	—
	Nialamide	100	209-241	—
	Nialamide	200	410-575	160/125
W.C.	——	—	62-111	190/140
	JB-516	25	506-632	140/110
	JB-516	50	586-825	—
	Nialamide	50	234	—
	Nialamide	100	392-422	—
	Nialamide	200	488-616	200/150
L.C.	——	—	45- 70	150/105
	JB-516	25	345-464	100/70
	Nialamide	50	103-119	—
	Nialamide	100	178-232	—
	Nialamide	150	332-438	—
	Nialamide	200	337-428	155/105

be valuable for those who are interested in the central effects of the MAO inhibitors in patients. In a preliminary comparison of our data with that of Dr. Nathan Kline it surprised us that quite independently we had both arrived at comparable figures on dosage; we, on the amount of drug needed to produce near maximal excretion of tryptamine, and he on the amount of drug needed to produce what he called the best possible effect in his depressed patients. That to me, if it can be substantiated, would seem to be an indication that there is a definite activity to relate to these MAO inhibitors based on their known biochemical property. With a test of this type making it possible to devise a regime of therapy which will have a chemically logical reason behind it, I think it should be possible to study and evaluate these drugs a little more systematically than has been done in the past.

I would like to conclude by giving an example in another area of chemotherapy. During the last war, there was a period when the efficiency of Atabrine as an antimalarial was questioned. With malaria the measurement of the clinical effectiveness of a drug is simple. But here, too, there were those who thought that the drug was excellent and others who thought it was not so good. With the advent of chemical methods for measuring Atabrine in tissues it was possible to show that what one needed was a very rapid attainment of a high maximum level of Atabrine in the blood and tissues, followed by a regime of therapy which would maintain the drug at a given level for a definite period of time. Once this was done it was found that in almost all cases Atabrine was a very effective antimalarial drug.

In mental disease we don't have anything quite as simple to measure as malaria parasites, but I think that if we are going to try to make comparisons from one clinic to another, between one compound and another (assuming that we are agreed that we would like to study the effects of MAO inhibition in mental disease) an attempt to relate these studies by some chemical means is necessary. Measuring the concentration of drug in the tissues is, in this case, not helpful because, as has been pointed out, these are drugs whose actions persist long after they disappear from the tissues. The next best thing, then, is to measure a known biochemical action of the drug which we associate with its central actions.

Effect of a Single Oral Dose of Two Aminoxidase Inhibitors in Normal Human Subjects

CARL PFEIFFER, PH.D., M.D.

We are conducting a study with hallucinogenic drugs in the Federal Penitentiary at Atlanta with 16 stalwart volunteers. We meet eight subjects on Tuesday and eight on Thursday and administer the drugs. We hope some day to find an antidote for LSD-25 or a drug which will attenuate or potentiate LSD-25. We are therefore interested in aminoxidase inhibitors such as nialamide because we hope later to combine these inhibitors with standard doses of LSD-25. Our subjects can differentiate reliably between 0, 25, 50, 75 and 100 gamma of LSD-25. They tend in general to underestimate drug effects so that one must give as much as 15 milligrams of D-amphetamine before they will admit that they've had an effective dose. Then they are apt to say that they've had "one or two leaves from a Benzedrine inhaler."

The volunteers are observed for three hours following ingestion of the drug. We have a report at that time as to what drug they had. They then write a 24-hour report on the drug. We have a morning urine analysis and a urine analysis the next morning and a complete blood count in the evening, which is 10 hours after dosing. So the data, then, that we will present by way of discussion is the trial of nialamide in a single oral dose of 125 milligrams, compared with JB-516 in a single oral dose of 36 milligrams.

Table 1 gives the blood pressure changes for 1, 2 and 3 hours, in 13 male subjects, after 36 milligrams of JB 516. There are no significant changes in systolic blood pressure or diastolic blood pressure. There is a tendency to increased pulse rate at the second and third hour, but this is not statistically significant compared to control levels. Table 2 summarizes trials in 15 subjects, with 125 milligrams of nialamide. There are again no significant changes in systolic or diastolic blood pressure. The rise in pulse rate, which is only a tendency (not statistically significant), tends to appear one hour later than with JB-516. The body temperatures will be discussed later.

Table 3 summarizes the subjective reports of the volunteers at the 3-hour and 24-hour interval. It is of interest that the most predominant effect of a monoaminoxidase inhibitor is extreme drowsiness in the 2 to 5 hour period after dosing. This was more evident with JB 516 and after stimulation also occurred more frequently with JB 516. Headaches

TABLE 1

Effect of JB-516 in Normal Volunteers

13 MALE SUBJECTS—36 mgm. JB-516

	Control	1 Hr.	2 Hr.	3 Hr.
Systolic B.P.	111.1	—3.8	—1.8	0.0
Diastolic B.P.	61.9	—1.0	+0.6	—1.3
Pulse	72.0	—0.3	+5.8	+3.2
Temperature	98.2	+0.18	+0.16	+0.13

TABLE 2

Effect of Nialamide in Normal Volunteers

15 MALE SUBJECTS—125 mgm. P-1133

	Control	1 Hr.	2 Hr.	3 Hr.
Systolic B.P.	111.5	—0.9	—0.8	—2.5
Diastolic B.P.	65.4	—1.4	—1.9	—3.2
Pulse	73.1	—2.3	+1.3	+3.7
Temperature	98.2	+0.05	+0.19	+0.15

TABLE 3

Subjective Effects of Single Oral Doses of Two Aminoxidase Inhibitors

	13 Trials 36 mgm JB-516	15 Trials 125 mgm Niamid
Sleep	9	5
Stim.	4*	1
After Stim.	4	2
Headache	2	4
Placebo	1	3
Nervousness	4	0
Anorexia	2	2
Sweating	2	1
Euphoria	1	1
Palpitation	1	0

occurred more frequently with nialamide. A placebo effect, wherein they report no effect insofar as mood or symptoms is concerned, was higher with nialamide. Nervousness occurred with JB-516, anorexia was equally frequent, sweating was more common with JB-516, euphoria was equally frequent, palpitation was reported only once—with JB-516.

Table 4 summarizes the effect on body temperature. Our subjects show a normal diurnal rise in body temperature and we therefore had to determine what the chance rise in body temperature would be in the 13 subjects who had had JB-516. We found no change statistically from the rise to be expected by chance. With the nialamide subjects we did find at the third hour a significant elevation of body temperature. And this brings up the question whether any rise in basal body temperature has been found with the clinical use of monoaminoxidase inhibitors.

TABLE 4

Change in Body Temperature from Initial Temperatures

	BODY TEMPERATURE 1 hr.	2 hr.	3 hr.
NDR Chance	+.07	+.16	+.01
(13) JB-516	+.18	—.02	—.03
NDR Chance	+.06	+.15	—.02
(15) Nialamide	+.05	+.19	+.15*

*P = <.02

(Figures in parenthesis denote number of patients.)

Table 5 summarizes the hematological findings. The blood count taken 10 hours after dosing shows, with each drug, a slight rise in hemoglobin, a slight rise in the white count, which is not statistically

TABLE 5

Changes in Hematological Findings 10 Hours After Oral Doses of Two Aminoxidase Inhibitors

	Hb. (Gm)	W.B.C.	Neut. %
1. Control (16)	14.02 ± .21	8.47 ± .62	55.8
2. JB-516 (15)	+0.14	+0.18	+3.5
3. Nialamide (13)	+0.09	+0.37	+2.0

	Lymph. %	Mono. %	Eosin. %	Bass. %
1.	38.1	4.1	1.94	0.125
2.	—4.3	—0.62	+1.0*	+0.615*
3.	—3.0	—0.53	+1.27**	+0.266

*Sig. P<.05 **Sig. P<.02

significant, and may correlate with the rise in body temperature. A leucocytosis usually accompanies a rise in body temperature. The neutrophils tend to be increased slightly, with nialamide and with JB-516. Lymphocytes tend to decrease. Monocytes are slightly decreased. Eosinophils are significantly increased with both JB-516 and nialamide. The same is true of basophils insofar as JU-516 is concerned. This is probably not a stress reaction. The initial reaction of an increase in neutrophils and a decrease in lymphocytes would be consistent with an epinephrine effect, but, the eosinophil count should fail. So one wonders if this is a drug induced effect rather than a general stress reaction.

In this brief study we have found that single oral doses of JB-516 or nialamide do not significantly alter blood pressure or pulse or normal human subjects. Nialamide may raise the basal body temperature of man, as is known to occur with aminoxidase inhibitors in the dog and rabbit. No deleterious effects were seen on hemoglobin or leucocyte levels but a redistribution of cells may occur, as shown by an increase in neutrophils, decrease in lymphocytes and rise in eosinophils and basophils. In general, the effect of single large doses is disappointing and the study indicates that this is the wrong way to use monaminoxidase inhibitors clinically. We did wish to see if anything could be ascertained by single large doses.

In studying the biochemistry of these inhibitors knowledge of the effect of an antidote would be useful clinically and even more useful for the theoretical studies.

A question I would like to ask Dr. Bloom is, "Has pyridoxine, or any other vitamin, been shown to counteract the monaminoxidase inhibition produced by nialamide?"

Transaminase Controlled Nialamide

THEODORE R. ROBIE, M.D., FELIX WROBLEWSKI, M.D.,
and EDWIN ALBANO, M.D.

Recent experience has proved that the amine oxidase inhibiting drugs can produce remission in a major portion of depressive states and it is our experience with one of these drugs, nialamide. Nialamide (Niamid-Pfizer) or N-isonicotinoyl-N'-B (benzylcarboxamide) ethyl hydrazine, is an antidepressant agent which has been reported to be effective in some depressed individuals who have failed to respond to other drugs and which, so far, has produced no serious undesirable side effects.

Whenever any new drug is prescribed it is imperative to safeguard the patient from any untoward effects. Since the liver is a vital organ intimately concerned with drug metabolism, it is important to know its condition not only before but also during continued administration of a new drug. It is fortunate that we now have a means of measuring liver damage with serum glutamic-oxaloacetic transaminase (SGO-T) determinations.

It has been shown that increases in the serum transaminase activity occur when there is liver cell injury or necrosis. This apparently is the result of the release of transaminases from damaged liver cells. The frequent measurement of this enzymatic activity can, therefore, be used as a warning of the development of hepatic necrosis. If this is discovered early the dosage of the drug may be reduced or its administration may be stopped in time to avoid generalized liver necrosis. Continued tests will indicate whether the hepatitis has been reversed and further therapy with amine oxidase inhibitors may be guided by routine SGO-T determinations. In a series of 23 cases reported in this paper, reductions in dosage were made on the basis of clinical improvement but SGO-T test results were at hand for guidance in planning the dosage schedule. Thus the patients had the benefit of a controlled dosage schedule of an effective new drug without risk of liver damage.

Interest in the use of nialamide logically followed from early experience with iproniazid after study of the latter drug for more than two years in patients with melancholia. The astonishingly good results with this amine oxidase inhibitor in the remission of depressive states and the consequent elimination of the need for electroconvulsive therapy in many of these patients has been reported.[3-8] When derivatives of iproniazid were synthesized it was of interest to compare them with the original drug and when other new amine oxidase inhibitors became available for clinical trial they were also welcomed. Whereas the report in April 1956 was concerned with a series of 100 patients receiving iproniazid, about one-fourth as many patients are now receiving nialamide and varying numbers of patients other antidepressants including Ro 5-0831, Ro 4-1018, Ro 5-0700 (Hoffmann-LaRoche) W 1544 (Nardil-Warner-Chilcott), Tofranil-(Geigy), and Deaner (Riker).

Results of Treatment with Nialamide

The present series of 23 cases in which nialamide is being used are summarized in the accompanying graphic tables. Dosage is shown by blocks, transaminase levels by x—x.

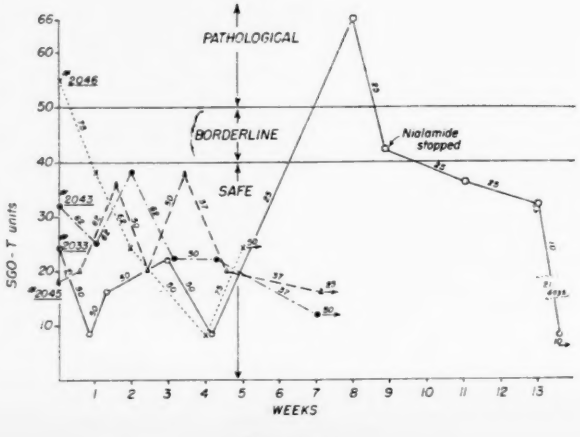

Figure 1.

Experience to date warrants reiteration of the assertion that the amine oxidase inhibitors are valuable and reliable antidepressants. Which one will prove to be the best is a moot question at this juncture. Perhaps another five or more years of research may be necessary before this question can be answered. At this point it can be said that there is sufficient evidence that nialamide is another good amine oxidase inhibitor which induces remission of depression, and apparently without serious side effects. Neither jaundice, nor other outward evidence of liver pathology has been encountered nor has any persistent hypotension or allergic edema or dermatoses been observed. However, smaller doses were used than those reported by other investigators and side effects may appear on increased dosages.

In the beginning most of these nialamide treated cases were started on a daily dosage of 50 to 70 mg. with dosage reduction within ten to twenty days. Whenever needed, dextroamphetamine sulfate (Dexedrine—Smith, Kline & French) 5 to 10 mg. a day was added if the patient was overweight, or methylphenidate hydrochloride (Ritalin—Ciba) 10 to 20 mg. twice a day if the patient was malnourished or of average weight, since the latter drug does not appear to reduce appetite. In one recent case, a woman whose melancholia was not clearing up as rapidly as hoped for, and who continued showing strong suicidal trends, daily parenteral administration of methylphenidate appeared to augment the effects of nialamide.

Case Reports (T.R.R.)

Case 1 (2044). A 34-year old housewife developed acute melancholia a short time after her brother was admitted to a state hospital for electroshock therapy. Her mental distress was accentuated by an acute virus infection (intestinal grippe) and by her strong belief that her mental breakdown must be of hereditary origin since her mother had also had a breakdown. If her supposition was correct, it should prove one of the best arguments for amine oxidase therapy since this very melancholy woman experienced a good remission of depression in less than four weeks. This occurred despite a single elevated transaminase value, which returned to low normal (20) a few days later without reduction in nialamide dosage. Circumstances suggest that the single elevated SGO-T test result was probably an artifact since none of the other five test results were above 20 units. On recent office visits, she laughed spontaneously and talked pleasantly in marked contrast to the severe persistent disconsolation evident in her first visits.

Case 2 (2046). One of the most satisfying improvements has occurred in a patient depressed because of multiple physical complaints that were considered hypochondriacal by various doctors. At each of her first six office visits during a five-week period, her gloominess and reiteration of the many physical complaints she had suffered with so long, were so emphatic that I despaired of any improvement from nialamide chemotherapy. Yet at her seventh visit after six weeks on this drug she walked in with a springy step and spontaneous smile, announcing, "Doctor, I am much better—I don't understand it but I am much better, and my appetite is so much better now. Oh, it seems so good to eat and enjoy food, because for nine months I've just crowded the food down with no relish at all."

There are some astonishing facts regarding this case. First, she is 82 years old and has had many of these physical complaints for the greater portion of her long life. Second, this improvement came about on the modest dosage of 62 mg. of nialamide reduced to 50 mg. in the second week of treatment because the elevated transaminase value (55 units before start of treatment) dictated caution. Yet there was a steady decrease in the transaminase level after the nialamide treatment was started (as shown in the graph on types of transaminase findings) from 55 before treatment down to 38 in the second week, 24 in the third week, 8 units in the fourth week and 24 in the fifth week. Is it possible that certain amine oxidase inhibitors may in some way induce improved liver function? Or, could it be possible that this chemical works with the vitamins administered with it in aiding liver repair?

Case 3 (2045). A very disconsolate 21-year old girl was brought for treatment by her father who was desperate because he feared that she was planning suicide. She insisted that she had been depressed all her life. Unfortunate experiences during the previous three years had undoubtedly accentuated her extreme melancholy status, a typical retarded depression. She had become involved with a fast set who were experimenting with mescaline and other drugs shortly after her divorce from a boy with whom she had lived only a few weeks after marriage. She, herself, was the child of a broken home, had no security during childhood, and had obviously sought security with the wrong man as a result of her inadequate immature judgment. Her own instability suffered further setbacks from associates who were unstable and inadequate.

Although it was presumed that electroshock therapy might become necessary, she was started hopefully on nialamide and it was astonishing to see the definite step by step improvement that became apparent as she returned at 3 or 4-day intervals. Before a week had passed, it was evident that EST would not be necessary, and in 10 days the 75 mg. dose of nialamide was reduced to 50 mg. Further improvement continued and the dosage was further

reduced to 25 mg. in the sixth week of treatment. Her transaminase test levels never rose above the 40-unit (safe) level. She has not maintained the 3-pound weight gain attained during the first two weeks of treatment, but this is not of major concern since her present weight is within normal range.

She has found a job and is already making plans for resuming the education which was interrupted by her premature marriage. A more wholesome outlook on life is being fostered during the psychotherapeutic conferences.

Chemotherapy is now an established medical procedure. The efficiency with which it is applied will depend entirely on the ability and training of the physician and the conscientious application of all the factors which enter into its use in fostering the betterment of mankind. In view of the fact that there is frequently a delay before a specific course of treatment is undertaken in our large state hospitals, it would seem that many depressives could be saved from further regression if one of the safe amine oxidase inhibitors were prescribed immediately upon the patient's arrival at the hospital. This suggestion is made after learning that one patient who was admitted to a state hospital, because she refused to carry out prescribed ambulatory chemotherapy or to accept ambulatory electroshock therapy, committed suicide by hanging four days after admission to the hospital.

A puzzling question which we may be asked by the melancholy patient is this, "Doctor, does the depression cause the unpleasant thoughts (mental conflicts) or do the unpleasant thoughts cause my depression?" The logical answer must be in keeping with our concepts of psychodynamics and based on the hypothesis that severe conflict can induce chemical change in the brain.

One patient believed that her depression came first and that this, in turn, initiated her mental conflicts which then produced the severe and incapacitating fears which had assumed dictatorial control of her behavior. Slow but steady progress is being made via insight psychotherapy enhanced by nialamide and methylphenidate hydrochloride (Ritalin) which have made intelligent discussion possible in place of the aimless and uncontrolled sobbing which filled her earlier conferences before the amine oxidate inhibiting effect had been instituted.

Fortunately, when the first patient was started on nialamide a policy had already been inaugurated of securing weekly Wroblewski SGO-T determinations during the first month, and thereafter as indicated, in all patients receiving antidepressant therapy. Although this takes time, since blood samples are taken during talks with the patient and many of them are centrifuged before transport to the laboratory, nevertheless, for the first time, a sense of security is assured in adjusting the dosage of the antidepressant drug up or down in accordance with transaminase findings. In our earlier observations, when treating patients with these drugs, we had only blood pressure readings, weight gains or losses and deep tendon reflex reactions as partial indicators for guidance in planning dosage schedules. But the newer amine oxidase inhibitors (including Ro 5-0831, W 1544 and nialamide) do not reduce the blood pressure significantly and do not induce the astonishingly rapid weight increase that was seen with the original iproniazid. Therefore, these clinical signs are no longer adequate as a guide with these compounds.

The brightest light that has appeared as yet to guide us is the transaminase test which has proved so valuable clinically in determining the presence of coronary infarcts. Since this is a supersensitive test it indicates the presence of slight liver necrosis long before other types of liver function tests. By reduction of dosage or stopping the drug, further liver damage can be prevented and, in most cases, repair will occur quickly permitting resumption of the drug in smaller dosages. By means of this test it has already been found, even in this small group of nialamide treated patients, that larger doses could have been safely prescribed and greater improvement might have been induced more rapidly.

There is certainly no reason why psychiatrists should not use this valuable test in amine oxidase inhibitor chemotherapy to determine the safe dosage levels in much the same manner that the internist uses weekly prothrombin time determinations for determining the proper dosage of dicumarol in cardiovascular disease. Dicumarol is not a drug to be prescribed without proper safe-

guards and the same holds true for amine oxidase inhibitors. During the seven-month period of this investigation, over 100 transaminase tests were made on 23 patients taking nialamide. Of these, only seven were elevated and in some instances there was the possibility that the elevated SGO-T level might have been an artifact.

Certain precautions must be noted. The blood sample must be kept under refrigeration. When a 24-hour interval (or longer) supervenes before the reading, there is possibility of error. It is exceedingly difficult to fulfill all the requirements necessary to completely prevent artifacts; however, in no instance was any jaundice observed when the transaminase was slightly or moderately elevated and in every instance the high reading had dropped before the next test was performed. This would suggest that very minimal liver involvement rarely persists even if the same nialamide dosage is continued, and it decreases quickly when the nialamide is discontinued. These facts suggest that the physician should not panic when he finds an elevated SGO-T value for any patient, but he should quickly reduce or stop the drug until the transaminase is again normal. Then the amine oxidase inhibitor can be resumed even in much decreased dosages. Obviously, when an elevated SGO-T occurs singly and high levels are not repeated in subsequent tests the chances are that it was an artifact which developed during the period between blood withdrawal and the completion of the test and there is a probability that no true hepatonecrosis exists.

It is important that the transaminase value be determined before commencement of therapy. This serves as a base level for later comparisons. The test should then be done once a week for at least four weeks and thereafter as indicated, usually at 10-day intervals for at least an additional month, then every three or four weeks.

Summary

This report is concerned with the use of nialamide in 23 patients with various mental disturbances. These include reactive depression, the manic-depressive, involutional melancholia, schizophrenia, psychopathic personality and barbiturate addiction.

On the basis of recent experience, it can be stated that nialamide is a good amine oxidase inhibitor which will induce remission of depression and apparently is free from serious side effects.

Dosages with amine oxidase inhibitors were adjusted to levels that would not produce serious liver damage. This was done by means of sodium glutamic-oxaloacetic transaminase (SGO-T) determinations.

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Nialamide for the Treatment of Anergy and Depression

MAURICE VAISBERG, M.D., CARL L. MCGAHEE, M.D., NADA RADINGER, M.D., and JOHN C. SAUNDERS, M.D.

The therapeutic efficacy and relative safety of monamine oxidase inhibitors have been established in the treatment of depression and/or anergy regardless of diagnostic category.[1-6] Among these, the preparation nialamide, as a result of a clinical study since November 1958, has shown clear indication that it is a rapid, safe, antidepressive and alerting agent.

This is a study of 21 white male and five female hospitalized patients with target symptoms of profound and persistent depression and anergy. They were selected on the basis of these symptoms without regard to diagnosis, duration of illness and previous treatment but mindful of their physical status.

A review of the history and evaluation of the presenting symptoms of the patients both before and during therapy were made. The following criteria were used in our evaluation: symptoms, duration of symptoms, diagnosis, number of prior hospital admissions, prior therapy, age, rate of response, time of therapy, adjunctive therapy, side effects and efficacy. All previous medication was discontinued one week prior to nialamide administration, a battery of baseline tests was made in the clinical laboratory and nialamide was started in those patients free of pathology. Medication was begun with exploratory doses in keeping with the thesis of a pilot project, i.e. to find the optimum therapeutic dose. The size of the dose was increased or diminished as indicated by daily observation of the patients. At regular intervals, the battery of biochemical tests was repeated. All other therapeutic modalities and milieu were constant.

The patients were started on 10 mg. of nialamide t.i.d. Through experience it was found that nialamide could be increased by weekly increments of 50 per cent in certain cases up to 150 mg. daily without any untoward effect. This observation was made from our studies with male patients. The male series was started in November 1958 and the female series in February 1959.

The 21 male patients varied in age from 21 to 60 years and the five females ranged from 30 to 76 years of age. Seven males were first admissions and 14 had from one to seven previous admissions. In the male series, duration of the present episode previous to admission was under six months in seven cases, from six months to one year in six cases, and over one year in eight cases. Approximately 40 per cent of the patients had been treated with other phrenotropic drugs without any significant help.

Diagnostic categories in the males included eight cases of schizophrenia, three of manic depressive psychosis, five of involutional psychosis, two of psychoneurosis, two of psychosis with cerebral arteriosclerosis and one of psychosis with mental deficiency. All five females were schizophrenics.

In addition to the target symptoms of anergy and depression, other discords present were confusion, thought disorganization, auditory hallucinations, suicidal ideation, somatic delusions, sensorial defects, paranoid ideation, tremors and social withdrawal. In addition to these, some of the females demonstrated one or more of the following: assaultiveness, compulsiveness, grimacing, grandiosity, ritualism and persecutory delusions.

Results

Three females showed mild improvement and two failed to respond. This may be due to the inadequate dosage (60 mg/day) and the short duration of therapy. Thirteen of the 21 males, within four to 30 days experienced a consistent and sustained improvement as manifested by complete alleviation of depression, increased verve and disappearance of inertia. Among this latter group, six improved within two weeks. The remaining seven improved after one month under the following conditions: four became

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The nialamide used in this study was supplied as Niamid by Chas. Pfizer & Co., Inc., Brooklyn, New York.

From Rockland State Hospital, Orangeburg, New York.

agitated and anxious requiring the addition of a phenothiazine with resulting stabilization of the antidepressive and alerting effects of nialamide, a single patient required an added time on original dosage for clinical response and two patients needed an increase in dosage. The most spectacular improvement occurred during the first week of therapy in two patients. Upon admission these two were completely disorganized, depressed, mute, frightened and immobilized with auditory hallucinations and persecutory delusions. In six and seven days respectively after administration of nialamide, 10 mg. t.i.d., both patients were fully alert, working, cheerful and practically free of delusions and hallucinations with considerable insight into their previous condition. One other male showed sporadic improvement and seven were either unimproved or worse. Two of those who became worse later improved with electrocoma therapy. Among the improved patients, four were completely cleared of delusions and hallucinations. In five more there was considerable alleviation of these abnormalities of ideation and perception.

Side effects were increased anxiety in two cases and akathisia in two others. These were relieved within a day by the addition of a phenothiazine. One patient developed a mild headache and nausea with a blood urea nitrogen of 22, one patient had transitory choreic movements and one had a transitory diarrhea. A syncopal attack was observed in one female patient. There were no other untoward actions observed.

One male patient with angina pectoris experienced no relief of pain with nialamide.

Improvement with nialamide had no apparent relationship to the duration of the present symptoms, the number of previous admissions, the diagnostic category, the secondary symptoms, the age of the patient, or to the severity of the anergy or depression.

See Tables 1-6 for analysis of clinical data on the patients treated with nialamide.

Although there are no absolute contraindications for the administration of amine oxidase inhibitors, we suggest that the administration be with great caution under the following conditions: previous history of liver pathology, renal failure, epilepsy, in topical application of cocaine since the occurrence of convulsive seizures is probable and as adjunctive therapy with thyroid preparations.

TABLE 1—COMPLETE REMISSION

(Male Patients on Nialamide)

Patient	Months of Symptoms	Number Prior Hosp.	Dx	Age	Days Until Response	Weeks of Rx to Date	Other Med.	Max. Mg. Daily	Notes	Side Effects
M.K.	1	4	M-D	51	35	26	—	90	—	T.D.
G.T.	7	4	M-D	55	10	10	—	30	—	—
R.B.	12	0	R-D	34	14	18	—	30	X	—

TABLE 2—MUCH IMPROVED

(Male Patients on Nialamide)

L.L.	3	1	M. Def.	25	28	26	P	30	X	AK
J.A.	2	1	S-Cat.	35	6	18	—	90	—	—
E.K.	3	7	S-Cat.	45	7	13	—	90	—	—

Summary

The psychic stimulant, nialamide, in a study with 26 hospitalized patients was found to be therapeutically effective, comparable to previously investigated monamine oxidase inhibitors. Nialamide was markedly

TABLE 3—STILL IMPROVING

(Male Patients on Nialamide)

Patient	Months of Symptoms	Number Prior Hosp.	Dx	Age	Days Until Response	Weeks of Rx to Date	Other Med.	Max. Mg. Daily	Notes	Side Effects
I.G.	8	1	S-Mx	26	14	26	P	90	X, MAO	TN, H, BUN
V.P.	60	1	S-Mx	27	21	26	P	60	—	AK
L.D.	7	0	Inv. M.	58	7	26	P	30	—	A
F.M.	12	2	Inv. M.	57	21	13	P	60	MAO	—
I.M.	180	2	S-Par.	48	28	21	—	75	—	—
A.I.	3	0	S-Mx	29	14	17	P	90	—	—
W.B.	4	2	Pn-D	51	14	13	P	90	—	—
I.H.	3	1	C.A.S.	60	21	13	—	150	—	—

TABLE 4—UNIMPROVED

(Male Patients on Nialamide)

O.S.	24	0	S-Cat.	21	–	14	P	90	—	—
P.R.	24	0	S-Mx	20	–	14	P	30	—	A
H.G.	9	1	Inv.M.	40	S	23	P	60	—	TC
J.B.	11	1	Inv.M.	44	T	7	—	90	—	—
F.B.	36	0	S-Mx	47	T	9	P	120	—	—
P.O.	120	1	M-D	50	T	7	P	150	X	—
L.W.	60	0	C.A.S.	56	?	22	—	90	?	—

TABLE 5—STILL IMPROVING

(Female Patients on Nialamide)

Patient	Months of Symptoms	Number Prior Hosp.	Dx	Age	Days Until Response	Weeks of Rx to Date	Other Med.	Max. Mg. Daily	Notes	Side Effects
A.S.	144	—	S-Par.	76	61	16	P	60	P,R	—
J.F.	96	—	S-Heb.	51	60	16	—	60	—	—
W.D.	12	—	S-Mx.	30	42	16	—	60	—	—

TABLE 6—UNIMPROVED

(Female Patients on Nialamide)

E.C.	12	—	S-Par.	41	—	16	P	60	P,R	—
J.S.	4	—	S-Par.	68	—	16	—	60	—	SYN

INTERPRETATION OF CODES ON TABLES

A—Anxiety
AK—Akathisia
BUN—Blood Urea Nitrogen elevated
H—Headache
MAO—Previously improved on a monamine oxidase inhibitor
P—Phenothiazine prior to nialamide
R—Reserpine prior to nialamide
S—Rx cut, lung cyst
SYN—Syncopal attacks with drop of Blood Pressure
T—Early improvement but given ECT
TC—Transient choreic movement
TD—Transitory diarrhea
TN—Transient nausea
X—Suicide attempt
?—Sporadic improvement, questionable drug related

effective in alleviating depression and/or anergy in 16 persons, restoring them to a higher level of psychic integration. Of the 16 cases, three were classed as recovered, five as much improved, and eight as improving. One patient showed sporadic improvement and nine were either unimproved or worse with nialamide. Side effects were anxiety and akathisia in a total of four patients which were quickly relieved by concomitant administration of phenothiazines. Four patients experienced either a mild nausea and headache, transitory choreic movements, a syncopal attack or transitory diarrhea. There was a slightly elevated BUN in one case. Later studies showed a transitory rise of alkaline phosphatase in one patient. There was no relief of pain in one case of angina pectoris. Evidence of postural hypotension was encountered in one patient. Nialamide appears to have little if any potentiating effect on other phrenotropic drugs. There were no serious untoward effects observed in this study. In addition to alleviation of the anergy and/or depression in 16 patients, there was a complete loss or marked lessening of delusional and hallucinatory content in nine of these.

From our data obtained in this exploratory study with nialamide, it is apparent that this monamine oxidase inhibitor is a safe, fairly rapid antidepressive and alerting agent; plus beneficient effects on ideation and perception. It alleviated the symptoms in approximately 60 per cent of hospitalized depressed and anergic patients without apparent relationship to the diagnostic category, the number of previous admissions, the duration of the present illness, the age of the patient, or the severity of the anergy or depression.

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Discussion

ALBERT A. KURLAND, M.D.

I am left with the thought that the clinical presentations so far seem to be missing a very important and vital aspect, which Dr. Impastato stressed at the beginning of this program, namely, the need for the clinician to be part of the research team. After listening to these presentations one begins to wonder with what part of the research team the psychiatrist identifies himself, since we are lacking good clinical descriptions of the depressions.

The effectiveness of the drug is indicated by the phamacological approach. We know that the drugs will affect some depressions but not others. How do we differentiate between these depressions? What types do we select to work with? Can we apply information gathered in other studies with a similar antidepressant to the present drugs?

We have been treating a small group of 17 hospitalized patients with a variety of depressive reactions with Nialamide. We have not seen the favorable results reported at this meeting. This may be a matter of dosage or manner of use, factors which we feel were not sufficiently stressed. We proceeded to build up very slowly to a level of 75 to 100 mgs. per day. This was done over a period of two or three weeks in patients that were treated for only a month. Our approach may have been over cautious because of concern relative to possible hepatic toxicity.

The factor of dosage, namely, the rapidity of administration and buildup may be, as indicated by Dr. Udenfriend, an extremely important matter. For example, with Atabrine, as Dr. Udenfriend has shown, if the dosage is not built up rapidly the antimalarial affect is not achieved. In the earlier studies with this drug there was a tendency to minimize its effectiveness as an antimalarial drug until the role of dosage was clarified.

The cataloging of patients by diagnoses while certainly a first step may not be adequate. Involutional melancholia, for example, may be of a retarded or agitated type, yet which one of these will respond better has still to be answered. In reviewing the literature on iproniazid and the other monoamine oxidase inhibitors and in attempting to obtain further impressions regarding the type of depression yielding best results the feeling prevails that the retarded, withdrawn, apathetic depression does better with these drugs than the agitated depression.

There are many questions that one would like to ask, and I am hoping that in the presentations to follow they will be answered. There is a need for information on the psychodynamics—what is going on between the patient and the doctor in these settings. Most of us will agree that the patient who is acutely disturbed and extremely suicidal or has a marked suicidal potential, as Dr. Impastato has indicated, is one with whom the clinician can't wait for the drug to take effect but must proceed more rapidly, namely with convulsive therapy. It is fortunate that the antidepressant monoamine oxidase inhibitors seem to indicate a range of activity with the depressed patient in whom the resort to convulsive therapy does not seem to be immediately indicated. In these patients we can administer a drug for a couple of weeks, hoping it will bring about a change in the patient's status. This again points up the need for good clinical descriptions of the type of depression in order to accumulate sufficient data to develop guidelines in our clinical approach.

The observation that there may be a relationship in the amount of tryptamine output in the urine in relation to the clinical effect of the drug is an extremely interesting point which has been emphasized by Udenfriend and Kline. How long after the administration of the drug does the change occur? How significant is this correlation? Where the drugs are effective are there any theories or explanations which might help in understanding the significance of this interval?

As a closing remark I would like to compliment the pharmaceutical manufacturers for doing a tremendous job in providing new drugs to work with, but I think in some ways we are letting them down because of the looseness of our own approach in drug evaluations.

Effect of Amine Oxidase Inhibitors on the Conditional Psychogalvanic Reflex in Man

LEO ALEXANDER, M.D., and and SUZANNE R. LIPSETT, B. A.

A year ago, in the course of a study of drug effects on conditional reflex activity, evidence began to accumulate that successful treatment with iproniazid was associated with a significant diminution in the conditional psychogalvanic reflexes to the excitatory and the inhibitory signals,[1] even in those cases (especially depressive states) in which the positive conditional psychogalvanic reflex was already markedly inhibited before treatment.[2] In most subjects the magnitude of the unconditional psychogalvanic reflex was also reduced. Since the fall of 1958, we have studied two other amine oxidase inhibitors, namely RO 5-0831/1 and nialamide (Niamid®) and found the same reduction of psychogalvanic responses in patients successfully treated with these new compounds.

This effect of amine oxidase inhibitors on conditional reflex activity was in contrast to the effects of successful electroshock therapy in that the positive conditional psychogalvanic reflex became increased in patients successfully treated with electroshock therapy.[3] It is also in contrast to the effect of successful therapy with meprobamate and benactyzine in combination (Deprol®) which brought about improved differentiation by decreasing the responses to the inhibitory stimuli, but did not significantly alter the magnitude of the positive conditional psychogalvanic reflex.[3]

The effect of amine oxidase inhibitors was surprisingly similar to that of chlorpromazine, which also decreased the conditional and unconditional psychogalvanic reflexes without altering differentiation between responses to the excitatory and those to the inhibitory signals.[3] This finding has theoretical implications with reference to the probable mode of action of these drugs upon the nervous system, as well as practical application to the problem of evaluation of adequacy of dosage.

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Method and Material

A conditional psychogalvanic reflex was established according to the classical Pavlovian method, by pairing a tone with an electric stimulus to the index finger, while another tone, presented in regular alternation with this reinforced tone at one minute intervals was never so reinforced. PGR measurements were recorded polygraphically throughout each conditioning session (which usually comprised 12 pairs of presentations) as described earlier.[2,3] The following four categories of psychogalvanic response were seen: response to the inhibitory conditional stimuli (CR—), response to the excitatory conditional stimuli (CR+), response to the unconditional stimuli (UR) and a generalized time reflex to the inhibitory tone patterned after the excitatory tone and its overlapping unconditional stimulus (GTR). These four PGR responses were measured as ohms drop in skin resistance for each pair of presentations of the tones for all patients before and after the administration of the drugs. The bar graphs included in this paper represent the averages computed for each conditioning session and the key to these graphs is shown in figure 1.

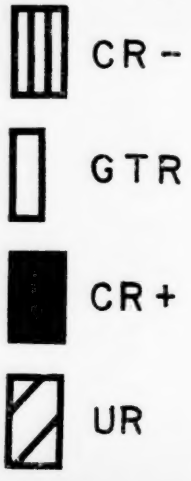

Figure 1.

The times chosen for the post-treatment re-tests were those at which emergence of clinical signs of response to the drug appeared or when treatment failure was established. Only patients are included in this analysis in whom a clearcut treatment result was achieved, either success (11 cases: five, full recovery; six, social recovery) or failure (four cases: two improved short of social recovery; two unimproved).

There were 15 patients included in this study. On predrug conditioning tests,[3] seven of these patients belonged to the inhibitory group, five to the average and three to the excitatory group. There were nine neurotic depressions, two psychotic depressions, one schizoaffective psychosis and three patients with severe and chronic obsessive-compulsive psychoneurotic reactions. Eight of the neurotic and one of the psychotic depressions were of psychasthenic-anhedonic type. Drugs used were iproniazid (Marsilid®), eight cases; an analogue of iproniazid, RO 5-0831/1, three cases; and nialamide (Niamid®), four cases.

The re-test times ranged from 20 to 284 days, the average being 70 days. Earlier re-tests were carried out from the sixteenth day onward in order to study the timing and gradual evolution of the change in conditional reflex activity, its relation to dosage, duration of its administration and clinical status of the patient.

Since the post-treatment tests showed diminution of psychogalvanic responsiveness in all three sub-groups classified by pre-treatment test pattern (excitatory, average and inhibitory) and for all of the three drugs tested, all groups were combined for purposes of study. The more stringent two-tail chi-square test was applied since the nature of the changes had not previously been postulated.

Results

Statistical analysis of the changes evident at the time of establishment of a clearcut treatment result after treatment with amine oxidase inhibitors showed that there was a significant quantitative diminution of responses to the inhibitory conditional stimuli (P=.008) and to the excitatory conditional stimuli (P=.008) without significant change in the differentiation between excitatory and inhibitory conditional stimuli (P=.608). There was diminution of the unconditional responses in the majority of the cases, slightly short of statistical significance (P=.058), but no significant change of the generalized time reflex (P=.266). (Table 1.) The three different drugs used all contributed equally to these results, the general quantitative reduction in the magnitude of the conditional psychogalvanic reflex responses being a characteristic of the action of all of them, minor quantitative differences and differences in timing of the change being related to the problem of dosage equivalents. In the entire group of 15 cases, there were only two exceptions to this trend: one patient showing a marked increase of the conditional and unconditional psychogalvanic reflex responses was a patient with schizoaffective psychosis who remained unimproved after adequate medication with iproniazid at a maximal dosage over a period of two months (fig. 2); while the other patient

TABLE 1

Amine Oxidase Inhibitors

(Iproniazid, RO 5-0831/1 and Nialamid)

N=15

	PGR AVERAGES IN OHMS		
	Before Drug	After Drug	P
CR—	1254	986	.008
CR+	2974	2108	.008
Ratio	4.17	2.07	.608
UR	5126	3484	.058
GTR	293	144	.266

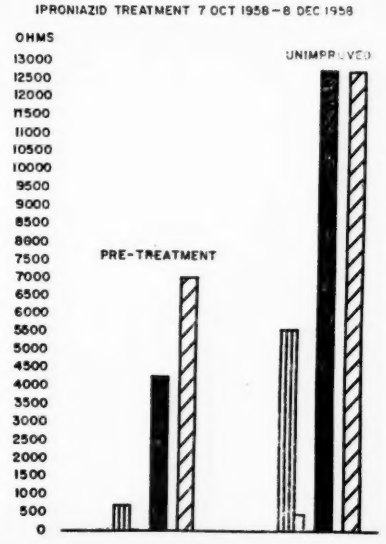

Figure 2.

showing only a slight increase in the conditional psychogalvanic responses was a patient with neurotic psychasthenic depression who achieved social recovery.

It is of interest that full recovery on treatment with amine oxidase inhibitors is consistent with marked reduction in responsiveness of the conditional psychogalvanic reflex. Figure 3 illustrates the change in response pattern in a patient with severe, totally disabling, obsessive-compulsive neurosis who achieved full recovery after three and one-half months of treatment with iproniazid after all other treatments which included prolonged analytic psychotherapy, a series of 33 electroshock treatments, 60 insulin comas combined with another series of nine electroshocks and treatment with a variety of tranquilizing drugs had failed. The pre-treatment test had shown an average type response pattern. The post-treatment test, done one month after consolidation of full recovery (which has remained sustained), shows the conditional psychogalvanic responses practically abolished and the unconditional responses greatly reduced in intensity.

Figure 4 shows the treatment induced change in response pattern in a patient with a similarly severe, chronic, obsessive-compulsive neurotic illness which had been of twenty years' duration and had been disabling for twelve years. This patient was treated by one of us (LA) for more than five years, treatments including psychotherapy, two courses of electroshock (18 electroconvulsive treatments) and a variety of tranquilizing drugs. Frontal lobotomy had been considered prior to initiation of treatment with an iproniazid analogue, RO 5-0831/1. In this patient, the pre-treatment test pattern was of inhibitory type. After social recovery, there was a further reduction of the conditional responses while the unconditional psychogalvanic reflex remained unchanged.

Figure 5 illustrates a case of depressive reaction with inhibitory pre-treatment test

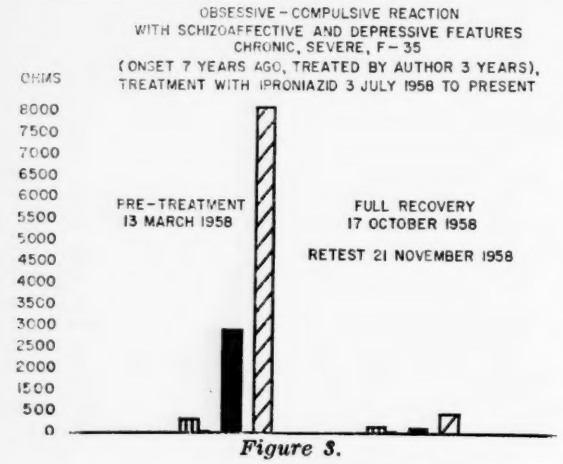

Figure 3.

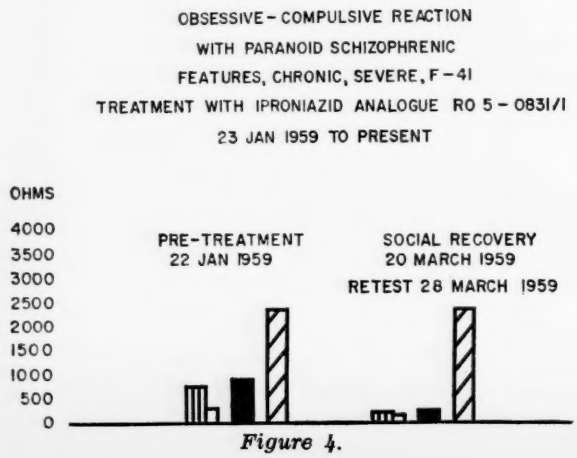

Figure 4.

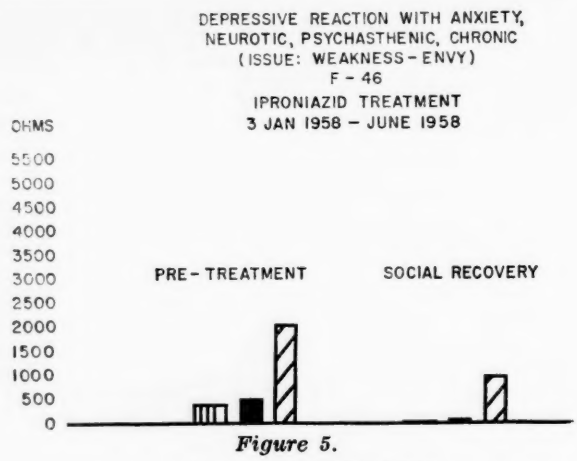

Figure 5.

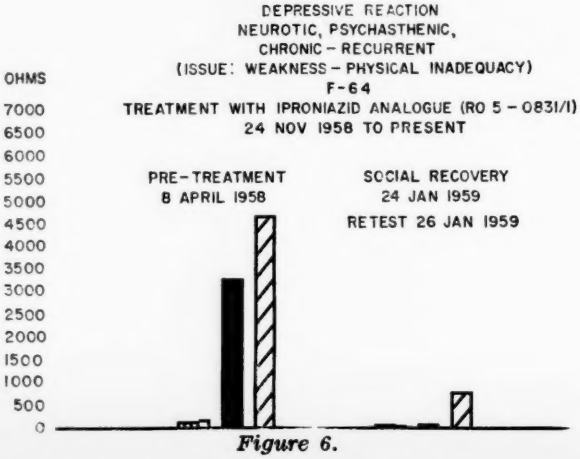

Figure 6.

pattern. Recovery following treatment with iproniazid was associated with almost complete abolition of the conditional psychogalvanic reflex responses, yet with well preserved differentiation. The unconditional psychogalvanic reflex was also reduced.

A similarly striking reduction of the evoked psychogalvanic reflex responses was observed in a patient suffering from chronic depression who had shown an average type of response pattern with excellent differentiation prior to therapy (figure 6).

Figure 7 shows the pre-treatment and post-treatment responses of a patient who achieved full recovery from a psychasthenic depression after treatment with Niamid. His pre-treatment test pattern fell into the excitatory response group. When re-tested two days after full recovery was achieved, marked reduction of all psychogalvanic reflex responses was evident. This diminution of the psychogalvanic reflex responsiveness was maintained concomitant with maintenance of full recovery status after the dose had been reduced by one-third. This case illustrates maintenance of reduced level of psychogalvanic reflex responsiveness in apparent relation to the clinical result, independent of the absolute level of dosage provided the dose is adequate to maintain clinical recovery.

However, when such a dose is insufficient to maintain clinical recovery, the psychogalvanic reflex responses increase pari passu with the relapse. This was exemplified by a patient who, after achieving a state of full recovery associated with marked reduction of psychogalvanic reflex responses, relapsed when the dose was subsequently gradually reduced to one-sixth (25 mg. iproniazid daily). When the patient was re-tested at that time, increase of psychogalvanic reflex responses to all stimuli was manifest.

While marked diminution of the conditional psychogalvanic reflex appears closely linked with successful clinical result, a moderate degree of diminution of the reflex may precede clinical improvement in the same manner as the less readily quantifiable increase in tendon reflexes and thus be an indicator that clinical results are obtainable. The therapeutic result may then be accelerated by raising of the dosage such as was done in the patient illustrated in figure 8. Moderate reduction of psychogalvanic reflex responses was observed ten days after the tendon reflexes had become hyperactive. Four days later, signs of clinical improvement became noticeable. The dose was then gradually doubled to 60 mg. (of RO 5-0831/1) daily over a three week period with full recovery supervening one week after doubling of the dose. Re-test after establishment of full recovery showed marked

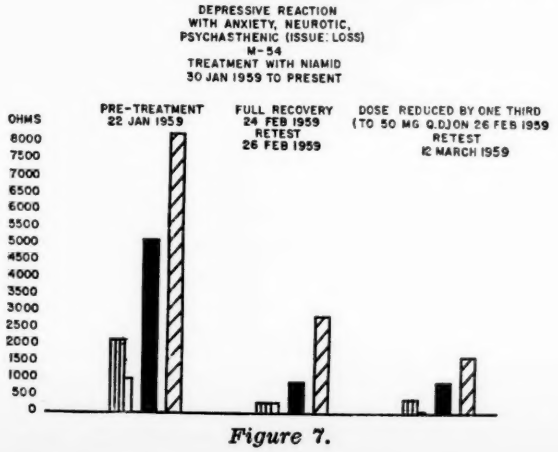

Figure 7.

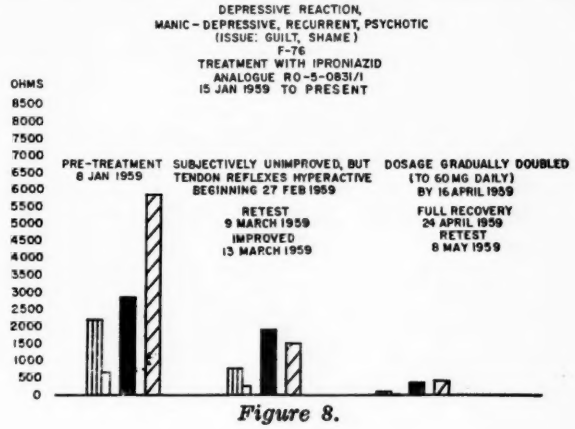

Figure 8.

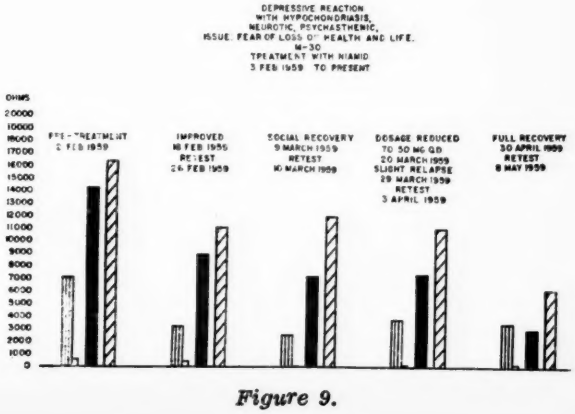

Figure 9.

reduction of all psychogalvanic reflex responses.

The gradual cumulative effect of the drug itself without raising the dose may be counted upon to bring about improvement in the course of time in less treatment resistant cases and this also reflects itself in the psychogalvanic reflex responses. Figure 9 illustrates this gradual progression of reduction in the magnitude of the psychogalvanic reflex in the course of time as therapy (in this case with Niamid) proceeds. This patient began to improve 16 days after initiation of treatment. Re-test eight days later revealed slight reduction of all psychogalvanic reflex responses. The diminution of the psychogalvanic reflex responses was found to have progressed further when the patient was re-tested the day after achievement of social recovery. The dosage was then reduced by one-third. This temporarily brought about a slight relapse which was associated with a slight increase of the conditional psychogalvanic reflex responses. However, without the dose being raised, the patient soon resumed improvement. When full recovery was achieved, there was a marked reduction of all psychogalvanic reflex responses. This case illustrates, on two distinct occasions, the cumulative effect of continued administration of the drug at the same dosage, first during the initial phase of the treatment and later after reduction in dosage had caused a slight temporary relapse.

Absence of change of psychogalvanic reflex responsiveness may be a helpful indicator of inadequacy of the initial dosage. The patient whose test responses are illustrated in figure 10 showed no diminution of the psychogalvanic reflexes and remained unimproved after 21 days on a dose of Niamid of 50 mg. q.d. The dosage was therefore raised to 75 mg. q.d. Twelve days later, the tendon reflexes became hyperactive and two weeks later the patient began to improve clinically. This clinical improvement was associated with a marked reduction in the magnitude of the conditional psychogalvanic reflex responses.

In another patient who had not responded to Niamid over a period of six weeks although the dose was raised from 75 mg. daily to 125 mg. daily, marked improvement and reduction of psychogalvanic reflex responses supervened nine days after the dose was raised further to 150 mg. daily, with full recovery established twelve days later.

Conversely, when prolonged treatment with an adequate dose of iproniazid is associated with maximal reduction in psychogalvanic reflex responsiveness but clinical improvement fails to materialize, this may be taken as an indication that such a patient is not likely to improve with further continuation or increase of the dose. Figure 11 illustrates the responses of such a patient who failed to improve in the course of nine and one-half months of iproniazid therapy. He subsequently achieved social recovery after 24 electroshock treatments. These enhanced the conditional as well as the unconditional psychogalvanic reflex responses in a manner characteristic for this form of treatment.[3]

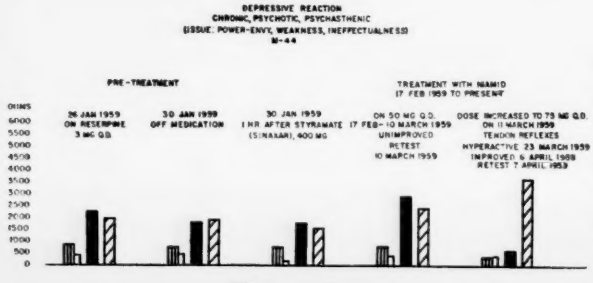

Figure 10.

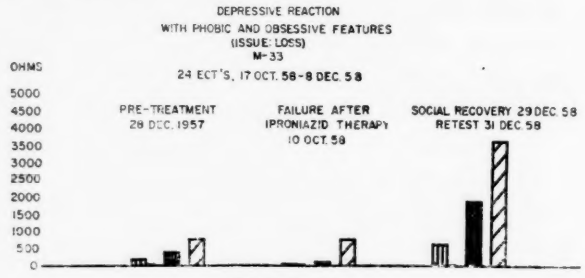

Figure 11.

Discussion

Theoretical Implications: The fact that amine oxidase inhibitors brought about a quantitative reduction of responses remarkably similar to that induced by phenothiazine derivatives, including chlorpromazine, was a surprising finding which may indicate that the favorable action of these two groups of drugs may result from quantitative reduction of interaction with the environment.

Responses to disturbing environmental influences may thus be reduced. This effect may have a relation to Eysenck's[4] concept of introversion and may be regarded as a protective drug-induced introversion. Chlorpromazine is known to accomplish this result by blocking the posterior hypothalamus.[5,6] There is reason to suspect that iproniazid may accomplish its clinical effects not by "energizing"—a concept quite inconsistent with Jacksonian physiology—but rather by blocking the anterior hypothalamus and thus releasing the posterior hypothalamus since many of its effects are remarkably similar to those seen in lesions of the anterior hypothalamus.[7] Both drugs, therefore, may reduce the hypothalamic discharges to the cortex, amine oxidase inhibitors those from the anterior hypothalamus and chlorpromazine those from the posterior hypothalamus. Thus both may increase the threshold for the cortical responses involved in the psychogalvanic reflex, especially the conditional, and also those in other processes of interaction with the environment.

Practical Application: One of the difficulties in the management of treatment with amine oxidase inhibitors is the wide range of effective dosage and the wide range of duration of administration of the drug necessary to produce a successful treatment result. Valuable time may be lost by continuing an ineffective dosage level too long and this may even lead to discontinuation of the therapy in potentially recoverable cases. Conversely, beginning treatment at too high a dosage may produce otherwise avoidable side effects. An objective quantifiable test for the effectiveness of dosage is therefore highly desirable. The conditional psychogalvanic reflex fulfills some of the requirements of such a test.

Early reduction in reflex activity allows the prediction that the dosage is effective and that, with time, will bring about a good therapeutic result.

If the diminution of the conditional psychogalvanic reflex is only moderate after relatively long time span, this may indicate the need of increased dosage in order to intensify and accelerate the treatment effect.

If there is no effect at all on the conditional psychogalvanic reflex after near maximal dosage over an adequate period, the dosage should be increased still higher (which can be done readily with the less toxic new compounds while with iproniazid this seemed inadvisable).

If an adequate dose produces near maximal reduction of the psychogalvanic reflex over adequate time, yet clinical results are not forthcoming, it can be judged that the treatment will not be effective and should be discontinued.

Summary

1) Successful response to treatment with amine oxidase inhibitors is associated with diminution in magnitude of the conditional psychogalvanic reflex responses without alteration in differentiation. In most cases the unconditional psychogalvanic reflex is diminished as well.

2) The neurophysiologic and psychophysiologic implications of this finding are discussed.

3) The diminution of the conditional psychogalvanic reflexes is related to dosage, duration of administration and treatment results.

4) Testing of the conditional psychogalvanic reflex is recommended as a means of evaluating adequacy of dosage with amine oxidase inhibitors.

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Discussion

DR. HERBERT FREED

Dr. Alexander's contributions to the field of objective psychiatry have always been of a pioneering nature. The material presented today emphasizes that he has found the psycho-galvanic reflex to be a sensitive indicator of the therapeutic responses to the monoamine oxidase inhibitor drugs. His perspicacity in selecting this psycho-galvanic reflex for his studies has been highlighted in the recent Adolf Meyer lecture by the brilliant English neurophysiologist, Gray Walter, who spoke on the high correlation between changes in the latency period of the psycho-galvanic reflexes and adaptive behavior, the term he prefers for learning. Probably the psycho-galvanic reflex will no longer be considered just a part of the lie detector test. It should be noted that Gray Walter correlated the latency period of the psycho-galvanic reflex with the learning process, while Alexander has correlated the drop in skin resistance, the phenomenon following the latency period. The change in the skin's resistance to the passage of electricity, its alteration in the barrier between the individual and the outside world, is found by Alexander to correlate with the successful use of the monoamine oxidase inhibitors. He had previously noted similar changes in the conditional reflexes in response of other patients to the phenothiazine derivatives. It was therefore suggested that the favorable action of these two groups may result from a quantitative reduction of interaction with the environment. As he says, the responses to disturbing environmental influences can thus be reduced. It is further suggested that iproniazid may accomplish its clinical effects not by energizing (a concept inconsistent with Jacksonian physiology) but rather by blocking the anterior hypothalamus.

I find myself in agreement with the authors in rejecting the concept of psychic energizers—not only because of the disagreement with the beliefs of Jackson and Sherrington, but also because the current psychodynamic formulations of Ostow, Kline and others, based on psychic energy distribution seem labored; the recent observations on imipramine (Tofranil®) admittedly not a psychic energizer, also makes the position less tenable.

In order to discuss the contribution more fully and to add a few comments on my limited experiences with nialamide (Niamid®), let me outline a heuristic formulation for the psychopharmacologic approach to the treatment of depression, realizing that your own Dr. Furst's recent contribution on the classification of depression differs from mine. It may seem very dogmatic and oversimplified, considering the multiple manifestations of the broad spectrum of psychiatry superimposed on the common denominators of sadness and lack of spontaneity. Loss or the threat of loss, or abandonment to the self, is the *psychobiologic core* of the depressive reaction. There is a *dual reaction* to this loss: (a) the *biologic* or *unlearned reaction,* characterized by impairment of thinking and a dulling of perception, both external and internal, with the aim of diminishing psychic pain, which is combined with (b), the *psychologic* or *learned reaction,* which is completely varied—it is an idiosyncratic reaction developed from the earliest years in response to deprivation and frustration; it is characteristically hostile and frequently accompanied by guilt; it may so color the previously mentioned biological aspect of the core reaction that agitation and/or anxiety appears in place of retardation.

It is recognized that it is occasionally impossible to be certain that the self has suffered loss or the threat of abandonment. The authors have looked for it in their patients, as noted here. Beside the numerous psychoanalytic studies which make the above heuristic formulation plausible for me, there is the observation on children, that their reaction to loss or the threat of abandonment is not manifested in a typical adult picture of depression until puberty—as well as the occurrence of the so-called "baby blues" in the post-parturient woman when the baby is no longer a part of the self.

Now Alexander has observed in a previous paper (1958): "The most consistent finding in depression was the marked impairment or absence of the conditional PGR." In other words treatment with the MAO inhibitors seems to maintain a state induced by nature, the state which Alexander has indicated could be one of insulation. I will concede that this type of defense may be ultimately healing. It would be compatible with my formulation of the biologic reaction—that is, the dulling reaction—affecting perception, thinking, and so forth, to lessen psychic pain. But with improvement it would seem plausible to anticipate changed psychobiologic responses, if at the same time psychic attitudes differ.

For example, I have been impressed by changes in perception, particularly focal attention, which may accompany mood changes. Patient A received nialamide and complained more bitterly about her subjective discomfort, the intensity of her anguish, after she had been on medication for a few weeks. She had not been responding to intensive psychotherapy and had heretofore refused any other form of therapy such as drugs. The nialamide in this case may have intensified her perception and made her feel more unhappy in the same way that the drug seemed to help another depressed patient, B, who said, "Up until the last few days people talked to me and I wouldn't pay any attention to them, now I can." It is important to note that in both cases a greater degree of emotional contact was made with the therapist and this must remain our primary goal in any treatment.

This accentuation of changes in perception is only one aspect of the alteration which we see occurring in the psychopharmacological approach. I find this compatible with the latest conclusions of Fink of Hillside Hospital, namely, the varied therapies are non-specific and produce an alteration in all aspects of behavior.

To return to the model for depression in relation

to psycho-galvanic reflex. The need to re-establish the learning process and to modify attitudes of guilt, and so forth, are of primary importance after establishing emotional contact. If it is possible to correlate the learning process with some aspect of the PGR, we have then a most valuable aid. Dr. Alexander has been an earnest student in studying what transpires during psychotherapy and during the learning process which is a part of it. So we must await his further observations.

In my 20 patients suffering with depression of varying intensity, seen both in a sanitarium (Rosen-eath Farm) and in private care, who have been given nialamide, the response has been favorable in half the cases. They have been observed for short periods, only from 1 to 5 months, and therefore the observations on a small number of cases for a short period of time can be considered only tentative.

I have been particularly impressed by the lack of disturbing side effects, such as posturnal hypertension, liver involvement, and so forth. Only increased tension, insomnia and anorexia have been noted by me as side effects. But the possibility does exist that the proper dose was not discovered for the particular patient, since in my cautious groping I have not given above 125 milligrams in 24 hours. Yet I have one patient who has apparently responded to a maintenance dose of 12½ milligrams a day. He insists that he can tell the difference when he takes a smaller or larger dose than this. An adequate trial of a placebo has not yet been made. For a situation like this the PGR technique would seem definitely useful.

Thus far from my clinical experience, in which I am not satisfied I am working in the optimal therapeutic range, the drug has not been as effective as electric shock, and possibly not as effective as imipramine. The need for more time to determine the effective dose necessitates a technique like Dr. Alexander's titrator, the PGR, and also that of the individualization of treatment, stressed now by the many psychodynamic psychiatrists who realize the value, symbolic and otherwise, that a pill can have for a patient.

Treatment of Depressive States in Ambulatory Patients

FRANK J. AYD, JR.,* M.D., EMIDIO BIANCO, M.D., and
LEONARD ZULLO, M.D.

Nialamide, a recent addition to the rapidly expanding list of chemical remedies for depressed states, is a potent amine oxidase inhibitor comparatively free of major side effects. Thus it may be used by general practitioners and other specialists besides psychiatrists, who seek to treat ambulatory depressed patients with a drug which is effective and, at the same time, safe. To demonstrate that nialamide fulfills these criteria, the results of a pilot study are reviewed.

Purpose and Scope of Study

To evaluate dosage, side effects, and therapeutic effectiveness, nialamide was prescribed for 100 ambulatory patients (65 women and 35 men, ages 22 to 72) whose essential complaints were: depressed mood, psychomotor retardation, loss of interest, feelings of guilt, insomnia, anorexia and functional somatic symptoms. These individuals were diagnosed: manic-depressive, depressed 32; involutional melancholia 17; schizophrenic reactions with depressive features 16; and neurotic depressions 36. This group comprised 64 patients without psychosis and 36 who were psychotically depressed.

The manic-depressive group comprised 15 patients with retarded depression, 13 with anxious depression and four with agitated depression. There were nine patients with their first, 17 with their second and 6 with their third depression. The histories of the 17 patients with their second depression revealed that with their primary attack four had had a spontaneous remission; three remitted with psychotherapy and ten recovered after electroconvulsive therapy (ECT). The six patients ill for the third time had received ECT for their second depression. Prior to the institution of nialamide therapy all had been ill for at least three months and 11 were considered candidates for ECT.

The involutional melancholics included one paranoid, six agitated and 10 retarded types. All were depressed for the first time. When selected for nialamide they had been ill from six to 24 months, had lost an average of 17 pounds, and were sleeping less than six hours a night. In this group were three chronically anxious patients whose involutional depression was characterized by intense anxiety and depression. They had received ECT which caused mounting anxiety and depression. They also had failed to respond to another amine oxidase inhibitor prescribed after they had not improved with ECT. In addition there were two chronic involutional depressives in whom repeated ECT had produced a transient elevation of the mood with no change in their melancholic ideation. For the remaining patient ECT would have been considered.

In the schizophrenic group there were five patients with schizo-affective, four unclassified, four paranoid and two pseudoneurotic reactions. Although they had been ill for years they were not deteriorated and their personality was relatively intact. They were chosen for nialamide because they were more disabled by the intensity of their depressive symptoms than by delusions or hallucinations.

In the neurotic depressive group were patients with neurotic and personality disorders with a past history of emotional instability or emotional lability. More than half of them had had previous depressive episodes treated with psychotherapy, drugs or ECT. These people were both anxious and depressed. In some there was a clear-cut relationship between their depression and a particular psychologic stress; in others the depressive symptoms appeared insidiously in the course of their chronic neurosis. In either case these individuals were more incapacitated by their depression than by their basic illness of personality disturbance.

Prior to nialamide therapy 75% of these patients were considered to have a good prognosis for symptomatic improvement with the ordinary antidepressive measures and 25% were assessed as poor prognosis.

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Read at a regular meeting of the Eastern Psychiatric Research Association held June 6, 1959, at the Waldorf-Astoria Hotel, New York, N. Y.

Nialamide is manufactured by Chas. Pfizer & Co., Inc., Brooklyn, N. Y., under their tradename Niamid.

Technique of Therapy

The most severely depressed patients were started on nialamide 25 mg. three times daily, while the mild, moderately ill patients were given 10 mg. three or four times a day. This dosage was continued for one week; then, if there was no benefit the daily dosage was increased at weekly intervals by increments of 10 to 25 mg. until improvement occurred or the maximum dose was 200 mg. a day. Thus, at the end of eight weeks treatment the maximum daily dosage was as follows: 50 mg., 10 patients; 75 mg., 44 patients; 100 mg., 32 patients; 125 mg., 5 patients; 150 mg., 5 patients; and 200 mg., 4 patients.

Because nialamide alone does not mitigate anxiety or insomnia, phenothiazine tranquilizers (Thorazine, Dartal, Trilafon, Stelazine or Tindal) and barbiturates were added whenever there was: (1) an acute onset of depression with features of anxiety, panic, agitation, anorexia and insomnia; (2) marked psychosomatic symptoms; (3) a paranoid coloring to the depression; and (4) when the depression immediately followed a severe physiologic or psychologic shock. Combined nialamide tranquilizer therapy also was routinely used for all depressed schizophrenics. In this study 75 patients received this combined therapy.

Therapeutic Results

Since nialamide was prescribed for the relief of target symptoms, benefit was determined by the degree of symptomatic improvement at the end of eight weeks' treatment. Hence, improvement indicates a 75 to 100% symptom amelioration; partial improvement means 25 to 75% symptom abatement; and unimproved or worse signifies less than 25% symptom relief or an aggravation of depressive symptoms. By these standards 21 patients were improved and 30 were partially improved. (Table 1.)

An analysis of these therapeutic results discloses that neither sex, age, nor duration or severity of illness influenced the outcome. Despite the fact that these patients resembled each other closely insofar as target symptoms were concerned, their therapeutic response was unpredictable and variable. Thus it is impossible to know beforehand who will benefit from this drug. Whether a depression was labeled neurotic or psychotic was unimportant, since there was no significant difference in the degree of symptomatic improvement obtained in either group. In this study 52% of neurotics and 51% of psychotics were improved.

TABLE 1

Niamid Therapeutic Results

Diagnosis	No. of Patients	Improved	Partial Improvement	Unimproved
MANIC-DEPRESSIVE, Depressed				
Retarded	15	3	4	8
Anxious	13	4	5	4
Agitated	4	1	2	1
INVOLUTIONAL DEPRESSION				
Retarded	10	2	3	5
Agitated	6	0	2	4
Paranoid	1	0	1	0
SCHIZOPHRENIC RELATIONS				
Schizo-Affective	5	0	2	3
Unclassified	4	1	1	2
Paranoid	4	0	1	3
Pseudoneurotic	2	0	2	0
NEUROTIC DEPRESSION	36	10	7	19
TOTAL		21%	30%	49%

When nialamide is effective some symptomatic response is evident between the first and second weeks of treatment, although there may be a therapeutic lag of four weeks before improvement is discernible. If a patient does not react to nialamide within two months the likelihood of improvement thereafter, even with very large doses, is slight.

To achieve therapeutic benefit 50 to 75 mg. nialamide daily is necessary. A few patients require up to 150 mg. a day. Larger doses may help an occasional patient, although the evidence to date suggests that dosage in excess of 150 mg. daily will not benefit a patient unresponsive to lesser amounts.

Combined tranquilizer-barbiturate-nialamide therapy is safe and free of any side effects from synergistic action. In this respect nialamide differs from other amine oxidase inhibitors which potentiate barbiturates and tranquilizer effects. This is fortunate because most patients require combined therapy to control such symptoms as anxiety and insomnia until nialamide takes effect. Thus, it permits uninterrupted nialamide therapy and partially accounts for the favorable therapeutic results obtained with this drug.

The 49 treatment failures included 29 patients whose pretreatment prognosis was good and 20 with poor prognosis. In this group were 16 patients who received nialamide for seven to 10 days only, after which ECT was administered with nialamide because they were severely depressed and potentially suicidal. The gravity of their illness precluded waiting for nialamide to take effect. These individuals received 128 ECT's while taking an average dose of 75 mg. nialamide daily. This combined treatment did not reduce the number of electroshock treatments required. It was safe. There was no evidence of potentiation of the preshock intravenous barbiturate and no hypotension, or cardiac irregularity in these patients. Combined nialamide-ECT produced a full remission in 14 of 16 patients treated.

The remaining 33 nialamide failures have been treated subsequently with other amine oxidase inhibitors. This resulted in improvement in only eight patients. This corresponds with clinical experience with other antidepressants which suggest that patients unresponsive to one amine oxidase inhibitor are often resistant to others.

A comparison of the therapeutic results obtained with nialamide and other antidepressants is listed in Table 2. This shows that, although therapeutically active, nialamide is less effective than other antidepressants used for the same target symptoms and assessed by similar criteria for benefit. The improvement rates with other antidepressants were: Tofranil, 72%; RO 4-1018, 60%; and Marsilid, 58.2%.[2,3] The improvement rate with nialamide was 51%.

Side Effects

To date nialamide has been singularly free of any major side effects. It has caused a minimum of minor somatic reactions such as: headaches (10%), dry mouth (4%), sweating (4%), dizziness (3%), constipation (3%), blurred vision (2%), hypotension (2%), epigastric distress (1%), and edema (1%). The majority of these side effects occurred with doses in excess of 100 mg. daily. In general they were mild and subsided with reduction of dose. In no case was it necessary to discontinue nialamide because of side effects.

A major drawback of amine oxidase inhibitors used as antidepressants has been their propensity to produce postural hypotension. For this reason nialamide is different from other amine oxidase inhibitors since this drug, even in doses of 300 mg. daily, which has been given to hospitalized patients, has not caused postural hypotension. Otherwise the blood pressure response to nialamide has been identical to the response to other antidepressants.

In contrast to other antidepressants, both amine oxidase inhibitors and non-amine oxidase inhibitors, nialamide has not caused diarrhea, delayed micturition, increased erotic desires, impotence, weakness and fatigue,

TABLE 2

Comparison of Therapeutic Results with Various Antidepressants

	No. of Patients	Improved	Partial Improvement	Unimproved
Tofranil	100	25.0%	48.0%	27.0%
RO 4-1018	50	24.0%	36.0%	40.0%
Marsilid	201	24.8%	33.4%	39.8%
Niamid	100	21.0%	30.0%	49.0%

TABLE 3

Side Effects Due to Antidepressants

(Side effect figures denote percentage)

	Niamid	Marsilid	Tofranil	RO 5-0831	SKF 385	RO 4-1018
Number of Patients	100	201	100	100	50	50
Headaches	10	19	15	12	17	18
Dizziness	3	46	36	40	48	54
Blurred Vision	2	27	20	26	23	29
Dry Mouth	4	50	42	36	40	50
Hypotension	2	9	6	7	7	8
Epigastric Distress	1	18	8	14	15	13
Constipation	3	56	40	10	16	18
Diarrhea	0	7	2	2	1	0
Delayed Nicturition	0	11	2	3	2	1
Decreased Erotic Desires	0	9	7	9	8	10
Impotence	0	3	2	1	0	1
Weakness and Fatigue	0	39	34	37	37	38
Edema	1	11	0	4	0	2
Sweating	4	11	33	9	9	7
Muscle Tremors	0	7	9	0	0	0
Dermatitis	0	4	2	1	0	0
Increased Psychomotor Activity	0	4	1	0	0	6
Hepatomegaly	0	1	0	1	0	2
Insomnia	0	9	3	5	11	4

muscle tremors, dermatitis, increased psychomotor activity, hepatomegaly, or insomnia. (Table 3.)

Routine laboratory tests of blood, urine and liver function in these patients were within the range of normal variation. Thus, in contrast to other antidepressants, nialamide has not caused anemia or any disturbance in renal or hepatic function.

Comment

Since the incidence of depression rises sharply after age 35, it occurs predominantly in patients who often have physical ailments such as hypertension or cardiovascular pathology and in geriatric patients with general intolerance for drugs affecting the central nervous system, including antidepressants. Because nialamide is well tolerated by patients in every age group and because it apparently does not cause postural hypotension this drug is safe for the treatment of ambulatory depressed patients. On the other hand a major drawback in nialamide is its slowness in taking effect. This drug should not be prescribed casually for depressed office patients who cannot be closely supervised and re-examined frequently. Careless use of nialamide, like the indiscriminate use of other antidepressants, could increase the hazard of suicide—an indictment not of the drug but of the prescribing physician.

Summary and Conclusions

Nialamide, an amine oxidase inhibitor, is a new antidepressant which was prescribed for 100 ambulatory patients (ages 22 to 72) whose essential complaints were depressive symptoms. There were 32 manic-depressives, 17 involutional melancholics, 15 schizophrenics with depressive features and 36 neurotic depressives in this study.

Severely depressed individuals were started on nialamide 25 mg. three times a day and moderately ill patients were given 10 mg. three or four times daily. If after one week there was no improvemnt the dosage was increased by increments of 10 to 25 mg. a day until improvement occurred or until the dosage was 200 mg. daily.

Phenothiazine tranquilizers and barbiturates were combined with nialamide whenever the depression was accompanied by anxiety, agitation, panic, anorexia and insomnia, marked psychosomatic symptoms, paranoid coloring, or when the depression immediately followed physiological or psychologic shock. This combined treatment also was prescribed routinely for all depressed schizophrenics.

Nialamide was given in conjunction with ECT to 16 suicidal patients. This combined treatment was safe but did not reduce the number of shock treatments required.

Side effects such as headaches (10%), dry mouth (4%), sweating (4%), dizziness (3%), constipation (3%), blurred vision (2%), hypotension (2%), epigastric distress (1%) and edema (1%) occurred with doses in excess of 100 mg. daily. These were mild and did not necessitate the discontinuation of nialamide. This drug did not cause postural hypotension nor many of the other side effects produced by other antidepressants.

At the end of eight weeks nialamide therapy 21 patients were improved and 30 were partially improved. Of the 49 treatment failures, 29 patients had a good prognosis and 20 had a poor prognosis. To achieve therapeutic benefit 50 to 75 mg. of nialamide daily was necessary. An occasional patient required as much as 150 mg. daily. Larger doses did not increase therapeutic benefit but were likely to produce side effects.

Although therapeutically active, nialamide is somewhat less effective than other antidepressants used for the same target symptoms and assessed by similar criteria for benefit. On the other hand because nialamide is well tolerated by patients in every age group and particularly because it apparently does not cause postural hypotension it is safe for the treatment of ambulatory depressed patients by general practitioners and specialists other than psychiatrists.

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Effectiveness and Tolerance of Nialamide for Geriatric Patients

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ROBERT C. BATTERMAN, M.D.

It is no longer theoretical that medications acting upon the central nervous system can favorably influence the mental, physical and behavioral status of patients. In the past decade, detailed studies upon the chemical mediation of central nervous system function and enzyme activity at cellular level have pointed the way for the introduction of drugs based upon these pharmacologic properties. With the advent[1] of monoamine oxidase inhibitors an important contribution became available to the physicians' armamentarium for the treatment of geriatric patients. However, as in the case of all new therapeutic agents it soon became apparent that preparations with a greater therapeutic range would be desirable. The avoidance of cumulative toxicity upon the liver, kidneys, blood forming organs and other vital tissues is the most important consideration for such compounds. The impaired function of these organs with aging contribute to the likelihood of toxicity with chronic administration unless the medications can produce the desired therapeutic effect with a dose well within the limits that can be handled by these degenerated and metabolically impaired organs. This report presents clinical data demonstrating that nialamide is of value for the treatment of depressed geriatric patients.

Selection of Patients and Method of Study

The effectiveness, tolerance and safety of nialamide were studied in both hospitalized and ambulatory patients. The hospitalized patients, inmates of a hospital for chronic disease, totaled 33 and consisted of two groups. The first group of 23 patients presented various degrees of impaired cerebral function on an atherosclerotic basis. This impairment was manifested by depression, disorientation, memory lapses and deficiency, lack of environmental interest, limitation of daily living activities, anxiety and in many instances a hostile attitude toward hospital personnel. Twelve subjects were male and 11 female. The age ranged between 48 and 84 with the majority over 71 years of age. Generalized arteriosclerosis was present in all. Nine subjects had in addition a cerebral vascular accident with hypertensive cardiovascular disease. None of the patients were in congestive heart failure.

The patients were carefully selected for this investigation since over a period of many months or years, their behavioral status was well established and more or less definite in pattern. Any change in the patients' status would thus reflect the possibility of therapeutic alteration rather than spontaneous fluctuation.

The second group of 10 hospitalized subjects with underlying neurological disorders such as parkinsonism, multiple sclerosis, Little's disease, muscular dystrophy, and organic brain syndrome were characterized primarily by an agitated behavioral pattern. In all other respects these 10 subjects were similar to the first group.

All subjects of both groups were evaluated for their physical and functional status with particular reference to cardiovascular, liver and kidney organs before inclusion in the study. The behavioral pattern was determined by three independent physicians as well as hospital personnel. Determinations of blood pressure, heart rate, complete blood count, routine urine examinations, thymol turbidity, bilirubin estimation and blood urea nitrogen were performed on all subjects before therapy and at weekly intervals at onset of study, and subsequently repeated biweekly. Patients were observed daily and their behavioral pattern reviewed every week.

Since we did not know the optimum therapeutic dose for nialamide, we progressively increased the dose until a desired therapeutic effect was observed. Thus initially the first eight subjects received 10 mg. as a single dose daily for 1 week. As experience with

nialamide was gained the dosage was increased. It was possible in the 23 depressed geriatric patients to evaluate six different dosage schedules for a total of 86 trials. Four subjects were observed for two dosage schedules, five subjects for three, one subject each for four and five trials and in seven instances, all six dosage schedules were studied. The duration of therapy for this group of patients ranged from four to 21 weeks of continuous drug administration. The majority of patients were observed for over 15 weeks. Two patients discontinued therapy because of epigastric distress after four and 13 weeks respectively. Two patients were discontinued because of hospital transfer.

The second group of 10 agitated hospitalized patients were observed for four to five weeks of continuous therapy on a single dosage scheme of 25 mg. three times daily. The follow-up on these patients was identical to that of the first group.

The ambulatory group of 20 patients consisted of 18 patients with anxiety states, one patient with a post-traumatic psychosis and another with excessive fatigue. Six were males and 14 females. The age ranged between 40 and 75 years with the majority over 60. Six dosage schedules from 10 mg. O.D. to 25 mg. t.i.d. were studied for a total of 39 trials. Duration of therapy ranged from one to 11 weeks with the majority treated for over six weeks.

Results

The effectiveness of nialamide for the depressed geriatric patient is presented in Table 1. Improvement in behavioral status was not noted until a dosage schedule of 10 mg. t.i.d. was used. However, an adequate response was not achieved until a daily dose of 50 mg. was given and not attained with significant predictability until 75 mg. daily was reached. At this time a higher dosage has not been used, but in view of almost complete lack of toxicity, it is possible that our studies have not reached an optimum dosage. The second hospitalized group of 10 agitated patients were not effected by 75 mg. nialamide daily. Whether this type of patient is unresponsive or a larger dose is necessary requires further evaluation.

TABLE 1

Results of Nialamide Therapy in Group I of Geriatric Hospitalized Patients

(Major Component Psychic Depression)

		Results			Untoward Reactions			
Dosage (mg.)	No. Patients	Excellent	Good	Poor	Constipation	Diarrhea	Epigastric Distress	Dizziness
10 O.D.	8			8				
20 O.D.	8			8				
10 t.i.d	20		5	15	3	1		
10 q.i.d	11		6	5	1	1	1	
25 b.i.d.	20	2	7	11	2		1	1
25 t.i.d.	19	4	10	5			1	1

In the ambulatory patients presented in Table 2, particularly those with the anxiety state, nialamide was relatively ineffective. With the highest dosage, used 25 mg. t.i.d., only four of the 11 trials show satisfactory relief from complaints. Again it is impossible to state whether the lack of response is due to dosage or type of patient studied.

TABLE 2

Results of Nialamide Therapy in Ambulatory Patients

(Major Component Anxiety)

		Results			Untoward Reaction		
Dosage (mg.)	No. Patients	Excellent	Good	Poor	Constipation	Diarrhea	Epigastric Distress
10 O.D.	1			1			
25 O.D.	6		2	4			
10 t.i.d	9	1	2	6			
25 b.i.d.	12		7	5			
25 t.i.d	11	1	2	7			1

In the treatment, regardless of group, a latent period of approximately seven days occurred before an effect became apparent. A priming dose, although in itself not effective, shortened the latent period for a subsequent effective dose.

Untoward Reactions

Regardless of dosage tried in the 33 hospitalized patients, untoward reactions were noted in 13 of the 86 trials for an incidence of 13.5 per cent. These untoward reactions were of a transitory nature noted after a total dose of 30 mg. daily was given and subsided in the majority of patients even though

nialamide was increased to 75 mg. daily. Only two patients discontinued therapy because of epigastric distress and only after four and 13 weeks respectively. The untoward reactions were predominantly gastrointestinal with constipation noted in six instances, epigastric distress in three, diarrhea in two, and dizziness in two. None of the patients had any change in blood pressure, in ventricular rate or in any of the laboratory tests followed for toxicological studies.

In the ambulatory group, only one minor untoward reaction was recorded. This consisted of nausea and epigastric distress with a total daily dose of 75 mg. after two weeks.

Discussion

The sense of well-being, increase in physical activity with participation in hospital routine, improvement in nutrition and mental alertness attest to the effiicacy of nialamide for the treatment of depressed geriatric patients. This beneficial action was attained with little or no cumulative toxicity. Our experience with agitated geriatric patients or with ambulant patients with the anxiety state was not satisfactory. It is possible that the optimum dosage required for the treatment of these particular situations has not been established.

Conclusions

Nialamide was studied in three groups of patients to establish dosage, effectiveness and safety. In depressed geriatric hospitalized patients, 25 mg. three times daily is sufficient for therapeutic effectiveness with minimal occurrence of untoward reactions. For agitated hospitalized patients and ambulant patients with the anxiety state, nialamide was not found effective with the 75 mg. dose used.

Treatment of Anergic Schizophrenia With Nialamide

PAUL E. FELDMAN, M.D.

Following the introduction of chlorpromazine in the early 1950's, many related compounds were developed which have proven to be uniquely effective in the treatment and management of the hyperactive, hyper-irritable schizophrenic. These tranquilizing drugs, however, have been disappointing insofar as their effect upon the withdrawn, regressed, inactive, apathetic schizophrenic was concerned. In fact, many of these retarded patients reacted adversely to these compounds, becoming more withdrawn and more inactive.

More recently, a newer class of compounds, psychic energizers, has been developed. These newer, compounds have been advocated for the treatment of depressive states. Their capacity to elevate mood, to remotivate depressed patients, to endow them with renewed interests and energy and to create a more desirable frame of mind has lead some of us to inquire why similar changes might not be effected by these compounds in the anergic schizophrenic.

With this premise in mind, we have been testing both monoamine oxidase inhibitors and non-inhibitors on anergic schizophrenics. Our initial experiences have been gratifying and has justified our continued investigation though at times the toxicity of the earlier compounds that we tested proved to be a powerful deterrent to our investiative enthusiasm. In our search for effective, nontoxic compounds of the enerizer type, one of the drugs that we have tested is nialamide (N - isonicotinoyl-N'-(B-N-benzylcarboxamido-ethyl)-hydrazine), and this report deals with the results that we have obtained.

Ten residents at the Topeka State Hospital, in training in the Menninger School of Psychiatry, provided a total of fifty, anergic schizophrenic patients from their services for testing with this compound. These patients were with but a few exceptions, chronic, treatment-resistant patients in whom the prognosis for improvement was poor. The test group had an average age of 41½ years and an average chronicity of illness of 14 years. There are approximately twice as many male as female patients. Most of them had proven resistant to chemotherapy and/or shock therapy or had failed to maintain any improvement induced by these modalities.

TABLE 1

Composition of Anergic Schizophrenic Group

Schizophrenic Reaction:	Number of Patients	Average Age (yrs.)	Aver. Duration of Illness (yrs.)	Male	Female
Undiff. Type	20	41	13	13	7
Par. Type	7	46½	17	5	2
Heb. Type	4	36	10½	4	0
Cat. Type	19	41½	14½	10	9
TOTAL GROUP	50	41½	14	32	18

I wish to emphasize that nialamide was administered, not as an isolated single, therapeutic tool but as part of a total treatment program. When patient-response made feasible the introduction of other treatments such as adjunctive therapy or psychotherapy, these procedures were employed to implement the treatment proram. From an operational point of view, our goal was to involve the patients to the greatest extent possible in a total milieu program.

This report cannot attempt to distinguish between those changes which were effected by the drug and those which might more properly be attributed to the total treatment program. However, I wish to reiterate that prior to receiving nialamide, these patients were considered treatment-resistant and had not responded to any of our previous efforts.

As a part of the test design all patients, before, during and following treatment received the following battery of laboratory tests intended to assess renal, hepatic and hemopoetic functions: indirect van den Bergh; alkaline phosphatase; thymol turbidity; cephalin flocculation; complete blood count and urinalysis including urobilinogen.

From Dept. of Research and Education, Topeka State Hospital, Topeka, Kansas.

This study was supported by a grant from Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

At the onset these tests were performed biweekly and after one month, bimonthly.

It was recommended to the participating residents that their patients be started on 30 mg/day; this dosage to be cautiously increased every three or four days until maximum therapeutic benefit had been achieved. Other than limiting the maximum daily dosage to 600 mg no other restrictions were imposed upon the schedule. Data has been collected on a variety of maximum dosage levels varying from 60 to 450 mg/day.

Patient-response to nialamide therapy was based upon the clinical evaluation of certain criteria covering those aspects of patient-behavior which appeared to be relevant to energizer therapy (Dress and personal hygiene; Interest in environment; Delusions; Hallucinations; Negativism; Hypo-activity; Hostility; Combativeness; Bizarre mannerisms; Appropriateness of conversation; Realistic planning; Amicability; Sociability; Participation in adjunctive therapy; Appetite; Sleep pattern; Tension; Self-mutilation; Compulsivity; Affect).

These criteria were assessed before treatment was started and at the completion of the study. In reporting final results, these items were rated by the resident evaluators on a 4-point scale. Items which were not applicable to a given patient were not rated so that a rating of "no improvement" in any of the criteria implied that the patient had some deficiency that had failed to respond in some degree to nialamide therapy. I then converted these individual criteria ratings into an over-all rating on a 6-point scale.

Ratings of "moderate improvement" or better were considered to be significant positive changes. Ratings of "worse," "no improvement" or "slight improvement" were considered non-significant changes.

Results

Table 2 indicates the dosage ranges which were employed, the average duration of treatment as well as the incidence of significant improvement at the various dosage levels. The results insofar as this study is concerned suggest that the effects obtained with modest dosages were better than those obtained with larger dosages. Note the difference between results obtained with less than 200 mg/day and those obtained with more than 200 mg/day. Obviously, this is only partly true since patients who responded early in the course of treatment were not subjected to the higher dosage levels.

TABLE 2

Dosage Range

Maximum Daily Dosage (mg/day)	Number of Patients	Aver. Duration of Treatment (days)	% Significantly Improved
60–100	15	59	66
100–200	5	84	100
200–300	4	96	50
300–450	26	82	31

The treatment of four patients was terminated prior to the completion of the study. In two of them this decision to terminate treatment was prompted by the abrupt development of serious suicidal trends; and in the other two because of the development of excessive tension, anxiety and antipathy towards the treatment. It may be worth noting that the two suicidal patients developed this trend on the service of the same doctor —and the same may be said of the two who became overly anxious. The untoward symptomatology of these four patients subsided promptly upon discontinuing nialamide.

Reasons for Terminating Nialamide Therapy Before Completion of Study

Patient	Reason	Maximum Daily Dosage (mg/day)	Duration of Treatment (days)	Resident
M.B.	Suicidal	75	13	Dr. C.
P.W.	Suicidal	75	16	Dr. C
W.D.	Anxiety	75	15	Dr. G.
C.K.	Anxiety	75	14	Dr. G

The absence of untoward drug effects was impressive. Only one patient developed what might be legitimately considered to be a drug side effect, and that was a case of excessive salivation. This occurred on 150 mg of nialamide per day and subsided when Kemedrin was administered. This patient did not show any other signs of parkinsonism. The total incidence of side effects, if the two suicidal and two anxious patients are included was 10%. If the suicidal and anxious patients are eliminated from consideration, the incidence of side effects is 2%.

The laboratory studies were essentially normal for a group of chronic schizophrenic patients. There were occasional elevations of one or the other laboratory tests—rarely did more than one test show elevation at a

time—and these elevations were neither consistent or persistent or related to any clinical findings. Clinically, there was no evidence of toxicity noted.

The patients began to show response to nialamide on approximately the 4th to 10th day of treatment. This response usually consisted of a conversion from inactivity to some state of activity. In some it manifested itself by a renewed interest in what was happening about them. In others it was apparent in their inquiry concerning their friends and families. Some of them, for the first time, began to write letters and to express a desire to have company. Patients who, prior to treatment, had been idle became involved in an increasing number of adjunctive therapy activities. The positive efforts made by some of the patients to resocialize were quite gratifying.

Table 3 indicates the over-all results obtained with nialamide therapy. Considering the chronicity of the group treated, we consider this a significant result. Approximately one-half of the patients showed significant over-all response to nialamide. Other than for the hebephrenic type, the response seems to be of about the same level of incidence.

TABLE 3

Results of Nialamide Therapy of Anergic Schizophrenia

	Significantly Improved No. Patients	% Patients
Undiff. Type (20)	11	55
Par. Type (7)	4	57
Heb. Type (4)	1	25
Cat. Type (19)	9	47
TOTAL GROUP	25	50

Table 4 lists the incidence of significant improvement in the criteria-of-evaluation in an order of decreasing effectiveness of response to nialamide. The relative order of these criteria is roughly the same as has been obtained with other energizers, and in keeping with this, nialamide intensifies and exacerbates hallucinations, delusions, hostility, combativeness, etc.

Discussion

The similarity of the anergic schizophrenic's response to nialamide and to imipramine is quite striking. Despite the fact that one is a monoamine oxidase inhibitor and the other a non-inhibitor, for all practical purposes, the results obtained are almost identical. Any differences in results may be accounted for upon the basis of subtle differences in the patient test-groups.

TABLE 4

Criteria-of-Evaluation Factors
Degree of Significant Improvement

	%
Hypo-activity (46)*	65
Bizarre Mannerisms (23)	57
Participation in Adj. Therapy (43)	54
Appetite (19)	53
Accessibility (42)	50
Interest in Environment (47)	47
Affect (46)	46
Sociability (39)	44
Appropriateness of Speech (45)	42
Amicability (34)	38
Negativism (33)	36
Tension (7)	29
Compulsivity (4)	25
Hallucinations (15)	20
Dress (26)	19
Delusions (27)	15
Sleep (10)	10
Realistic Planning (27)	8
Self-Mutilation (2)	0
Combativeness (4)	0
Hostility (8)	0

* Figure in parenthesis indicates number of patients displaying pathology in the various criteria.

The effects of nialamide and imipramine are also similar in respect to the individual criteria-of-evaluation. In both, approximately one-half of the patients show a significant response in the first six criteria.

Comparison of Nialamide and Imipramine

	% Sig. Improved Nialamide	Imipramine
Schizophrenic Reaction:		
Undiff. Type	55	54
Par. Type	57	53
Heb. Type	25	0
Cat. Type	47	41
TOTAL GROUP	50	48

In this series 3 patients had previous trials with other energizers and tranquilizers. Table 5 indicates the comparative responses that were obtained. W-1554 is now known as 'Nardil'. I do not know whether the other two energizers have been assigned trade names. In this table, a difference of ± 2 is considered significant. In this particular test group, the superiority of energizer therapy over tranquilizer therapy is evident. The effectiveness of nialamide and imipramine

Comparison of Criteria-of-Evaluation

Factor	% Sig. Improved Nialamide	Imipramine
Interest in Environment	47	59
Appetite	53	58
Affect	46	52
Hypo-activity	65	68
Participation in Adj. Therapy	54	49
Accessibility	50	47
Conversation	42	44
Sociability	44	43
Negativism	36	30
Amicability	38	28
Delusions	15	16
Hostility	0	13
Combativeness	0	10
Hallucinations	20	4

seem to be on a par and both are definitely superior to the other three energizers listed.

The results of this study suggest that nialamide therapy is of value in the treatment of anergic schizophrenia. Most impressive, in this study, considering our experiences with other hydrazines in the past, is the almost complete absence of toxicity and untoward effects. Though we were alerted to the possible development of orthostatic hypotension, constipation, hyperreflexia, paresthesias, vertigo, etc., these side effects were not encountered.

Nialamide definitely activates some of the inactive schizophrenics but only infrequently to the extent that the activation is considered excessive. It does, however, exacerbate delusions and hallucinations in a manner similar to that encountered with other energizers. Whereas, with imipramine, this exacerbation of projective phenomena and hyperactivity necessitated the incorporation of a tranquilizer to the treatment regime, this was not found necessary with nialamide therapy. It was our impression that patient-response to nialamide was a little slower than with imipramine.

It is our opinion, upon the basis of this study, that nialamide does effect desirable changes in some anergic schizophrenics, and though there is no evidence to suggest that this change involves any basic alteration in the underlying psychopathology, the changes created are conducive to the introduction of more definitive, therapeutic measure which were not feasible before the patients received this treatment.

Even though our results as recorded indicate exacerbation and intensification of certain projective symptomatology, this in no way is meant to imply that these patients are sicker—to the contrary, it can be very logically demonstrated that this development

TABLE 5

***Comparative Responses** (Over-All Improvement)*

(Pt providing own baseline)

	ENERGIZERS					TRANQUILIZERS				
Pt.	P-1133	G-22355	W-1544	Ro 5-0831	SKF 385	Reserpine	Thorazine	Pacatal	SKF 4579	Win-13,645
L.A.	3	3	0	2	0	0	2			
G.A.	3	4	0	1	0	1	3			
S.B.	3					0	1	1		0
M.B.	0		0				2	4		
J.C.	3	3	0		0		1	0		
P.D.	3	3	1			0	1			2
W.D.	0	0	0			0	0	0		
F.D.	0	4	1		0		1			
F.E.	4		0				2	0		
A.F.	1						0	0		
K.F.	3	3	0	1		0	1	0		
L.H.	4	3	0		0	0	1	0	1	
E.J.	2	2			0	0	0	0		
O.K.	3		0		0		2	1	1	
A.L.	3	3								
G.L.	2		0				1	0		
E.L.	4	3	1	1	0	1	0	1		
B.L.	3	3		1						
G.M.	4	5	0		0					
I.M.	4		2				1	2		
J.M.	4				1		0	3		
H.M.	2					0	0	0		
T.P.	3				0		0			0
R.P.	3	2			0		1			
B.S.	3	3	0		0		1			
B.S.	2	4	2		1		0			
M.S.	3		1			0	1			1
R.S.	2	3	0		1			0		
P.W.	0	1					1		1	
D.W.	4	3	1		1			2		
A.W.	3	3	1		0			0		

P-1133: N-isonicotinoyl-N'-(B-N-benzylcarboxamido-ethyl)-hydrazine (Niamid).
G-22355: Imipramine HCl (Tofranil).
W-1544: B-phenylethylhydrazine HCl (Nardil).
Ro 5-0831: 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine.
SKF-385: Trans-dl-2-phenylcyclopropylamine HCl.
SKF-4579: 10 - (3-dimethylaminopropyl)-2-methyl phenothiazine HCl.
W-13,645: 8-(3-[10-(2-chlorophenothiazinyl)] propyl)-3-hydroxynortropane ethanesulfonate.

0=No improvement
1=Slight Improvement
2=Slight to Moderate Improvement
3=Moderate Improvement
4=Moderate to Marked Improvement
5=Marked Improvement

(Difference of 2 is significant)

Criteria Used to Evaluate Patient-Response to Nialamide Therapy

Dress and Personal Hygiene	Realistic Planning
Interest in Environment	Amicability
Delusions	Accessibility
Hallucinations	Sociability
Negativism	Participation in Adjunctive Therapy
Hypo-activity	Appetite
Hostility	Sleep Pattern
Combativeness	Tension
Bizarre Mannerisms	Self-Mutilation
Appropriateness of Conversation	Compusivity
	Affect

is a step in the direction of better mental health for these patients; despite the fact that this may increase the demands upon the therapist and other hospital personnel.

It may very well be that we have tested a heterogeneous group of schizophrenics in this study. Perhaps anergia in itself is an inadequate screening criterium and some more sensitive method of selecting schizophrenics for energizer therapy might delineate the types of patients who might respond in a greater percentage of the trials.

What is needed is some more sensitive screening technique. Physiological screens such as the Funkenstein and Thorn tests have proven disappointing as they do not distinguish reactors from non-reactors. In general the search for a sensitive, accurate physiological screen for this purpose has been unrewarding.

Perhaps, we may have to resort to some sort of psychological screening technique for the key to the energizer-reacting schizophrenics. At the moment the prospects seem brighter for differentiating this type of schizophrenic by their ability or potentiality for developing object relationships. This is a matter for future investigation and we hope might separate the schizophrenic energizer-reactors from the non-reactors.

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Discussion

DOUGLAS GOLDMAN, M.D.

The presentations of Drs. Ayd, Mouratoff, Feldman and their respective co-workers are interesting in a number of ways. The data reported should be our chief interest, but several aspects of exploratory clinical drug evaluation research are well illustrated and deserve some discussion as well.

The results of early studies cannot be considered in too critical a manner since they follow tentative, groping work, and cannot show mature organization and classic flourish. They can, however, indicate stresses involved in this relatively new subspecialty in the field of medicine: organized search for effective new weapons against human illness.

The increasing differentiation of functions in medicine has brought us to a point where those who are clinically engaged have little in common with those who delve in chemical and pharmacological laboratories, and even the latter are drifting farther apart. The prime function of conferences such as this is therefore one of liaison to bring about some interdepartmental understanding. In no phase is this more important than in the development of clinical knowledge and technique, particularly in psychiatry, a field beset by doctrinal bias and distortion, and insufficient foundation in basic biologic sciences. We may, therefore, flatter ourselves, slightly to be sure, that these studies began with a chemical-biologic idea to test against clinical illness, rather than from pure empiricism and accident. It should not at this time, however, be concluded that we have enough evidence to think that any mental disease has a chemical or enzymatic mechanism.

In the clinical area, there is lacking any adequate principle or group of criteria, to differentiate the illnesses into more specific entities than those set up more than fifty years ago on purely observational and empirical grounds. It is not surprising that effects of drugs are unpredictable when even experienced clinicians have only Kraepelin and Bleuler to fall back on for differential diagnosis.

It is undoubtedly going to be of value to the development of a more scientific point of view in psychiatry, that for development of new drugs pharmacology has invaded the area of experimental animal behavior. We have not recognized as yet, more than the most embryonic principles that can be translated from animal to human terms. It is to be expected then, that the preclinical data that we receive to entice us into investigation of any drug will not be adequate to define strictly the usefulness of the substance, if indeed it has any.

We have from bitter experience learned something of toxicity in the human subject as it relates to chemical structure and laboratory activity, but in the areas of hematologic and hepatic function animal work, even with obviously excessive dosage, does not serve to predict effect in man. It is, therefore, to be expected that dosage in early work will be timid and confused, since the lessons of earlier studies are not quickly forgotten and only slowly guide us to secure techniques.

The choice of patients and their classification is an important element in determining drug effect. To the unsophisticated all psychotic individuals are alike, but to the perceptive clinician differential characteristics make classification, if not diagnosis, possible. In drug studies therefore, such pseudo-differential terms as "ambulatory" vs. "hospitalized," "psychotic" vs. "neurotic" should really not be used in a diagnostic sense. A patient on leave from a state hospital is as ambulatory as the university professor or business executive who is receiving treatment for depression while continuing at work. In Puerto Rico I saw grossly psychotic schizophrenic individuals managed as out-patients and recovering with the help of drugs.

The fundamental bias of the physician is of more importance in psychiatry than in any other specialty of medicine. Only improved knowledge of the relationship of cerebral physiology, neurologic connections and mechanisms, and their relationship to clinical states can "burn off" the fog of pre-occupation with thought processes, personal relationships, and the unconscious. Some physicians have left their basic physiologic and pharmacologic training so far behind that in treating psychiatric patients they are interested only in "the meaning of the drug to the patient," not its effect and therapeutic value.

To consider the authors' presentations individually:

Dr. Mouratoff and his co-workers have studied a heterogeneous group of organically sick patients. Such patients can contribute clearly only to knowledge of toxicity. Failure to improve in such a group does not constitute an indictment of the drug. In the ambulatory patients with anxiety states more clinical differentiation and higher dosage levels would no doubt have produced better effect. The minimal side effects observed were not necessarily in any sense pharmacologic.

Dr. Ayd and his colleagues have made a different kind of study of the effect of nialamide, probably more sharply oriented to its possible usefulness in alleviating depression. He notes the depressive symptoms that he sought to relieve and dosages given. The dose level here tended also to be properly cautious. Combinations with other drugs tend to obscure actual results, but in a practical sense are called for under conditions encountered in private practice. The need for electroshock treatments described by Dr. Ayd seems different in combination with nialamide than with other antidepressants in our experience. We have found the number of electroshock treatments much diminished when antidepressants were given. His patients showed fewer side effects than with other antidepressants. This will be noted in comparison with our data. Nialamide produced side effects similar to other hydrazides in his series, but differed with those from imipramine. It is also to be noted that in his depressed group of patients, nialamide produced improvement equal to that produced by other hydrazide compounds. It was in the schizophrenic group that results were poor, but this is true of any antidepressant.

Dr. Feldman's report is interesting in that the choice and management of the patients under study was turned over (relegated) to psychiatric residents, whose immaturity and doctrinaire bias would put a burden on study of any drug effect. The concept of "anergic schizophrenia" is, for me, difficult to appreciate. Many pitfalls were evident in Dr. Feldman's report which required reading of the numbers in the parentheses which in Table 4 were often much smaller than the total number implied in the % column. I would vigorously disagree with any statement that implied that any chronic schizophrenic reactions respond more effectively to "energizers" than to "tranquilizers"—assuming both kinds of drugs to be properly chosen and adequately administered.

Experience at Longview State Hospital to date includes 33 patients treated with nialamide. The results with our patients indicate that the drug is an effective antidepressant drug, with good antidepressant effect similar to other hydrazides and imipramine. We cannot yet set up an order of effectiveness. Important side effects in our experience have been about as frequent as with other antidepressants, but the hypotensive effect seems milder. Of 17 patients treated long enough by April 11 to determine possible hypotensive effect, five showed a fall of 20 mm. in systolic pressure, and four dropped to 90 or below. This is similar to the experience with other amine oxidase inhibitors.

We have to date had no instance of hepatic toxicity with any of the hydrazides, and our series of patients is over 350.

TABLE 1

Effect of Antidepressant Drugs in Schizophrenia

	Schizo.		Affect.		Other	
	Total	Worse	Total	Worse	Total	Worse
Marsilid (Iproniazid)	64	21	48	7	44	4
Nardil (W-1544)	19	6	9	1	19	3
Tofranil (G22355)	25	8	22	2	36	4

One common almost universal effect of antidepressants not stressed today, except silghtly by Dr. Feldman, has been the arousing of latent or aggravating of overt schizophrenic manifestations. Table 1 illustrates the capacity of other antidepressants to worsen schizophrenia. Nialamide to date has an entirely similar effect. In ambulatory, unsupervised patients this can be critical.

In closing, I would caution that the number of patients studied is too small and the period of study too short to reveal all of the possible difficulties to be encountered—or on the other hand perhaps, all of the benefits.

A Trial of Nialamide in Chronically Ill Mental Patients

JACKSON A. SMITH, M.D.

The patient's history is one of the important factors in the evaluation of any treatment procedure. The history should reveal the duration of the illness, the response to previous treatment, likelihood of spontaneous remission, and an estimate of the patient's pre-morbid adjustment.

Zubin found that more than 80% of the patients discharged from mental hospitals, depart by the end of the first year. This indicates that any method will be more effective when tried on patients ill less than one year.

The chronically ill patient is a problem. Kramer showed that the probability of release after two years of hospitalization was no greater in the 1946-1950 interval than between 1916-1925. Undoubtedly many chronic patients have improved sufficiently with the use of tranquilizing medications to be discharged; but this does not fully explain the over-all decrease in the population of state hospitals.

We should always be alerted to changes which occur in the natural course of the illness. If we neglect this the development of an agitated or more disturbed state may erroneously be attributed to the drug being tested rather than to a change in the illness.

The Patient Group

Of the 26 patients included in this study 15 were males and 11 females. All were schizophrenic. They had been refractory to previous therapeutic efforts, which had included one or more of the following: metrazol convulsions, insulin coma, electroconvulsive treatment, tranquilizers and "energizers." The majority were apathetic, withdrawn, bizarre and inappropriate.

During the study all patients remained on the ward where they were then resident. The only change in personnel was the addition of a psychiatric nurse who recorded their behavior and blood pressure.

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It should be added that the hospital where this study was done has been participating in drug evaluation projects since 1955 and the trial of a new compound has become a routine event. The drug studies are carried out by members of a research unit. The personnel of this unit (three psychiatric nurses, a technician and a secretary) have no service function but are continuously involved in treatment evaluation.

TABLE 1

Time in Hospital

Over 1 year	1
Over 2 years	2
Over 4 years	1
Over 5 years	21
Total patients	26

Average hospitalization—17.2 years

Table 1 shows the years of hospitalization. Twenty-one had been hospitalized over five years and none less than one year. The average years of hospitalization for the group was 17.2 years.

TABLE 2

Age of Patients Treated

25-34	2
35-44	5
45-54	13
55-64	6
Total patients	26

Average age—49:4 years

Table 2 shows the age range was between 27 and 63 years. The number in each ten year interval is also shown.

Procedure

The medication was given orally, with an initial daily dose of 30 mgm. during the first week, 50 mgm. daily during the second week, 75 mgm. during the third week. During the last three weeks the daily dosage was increased by 50 mgm. each week (4th week 100 mgm., 5th week 150 mgm., and final week 200 mgm.). The study covered six weeks.

Method of Evaluation

A standardized form was used in recording behavioral change. This form is composed of three sections as shown in Table 3.

TABLE 3

Section of Evaluation Form Used in Recording Behavioral Change

1. Brief history and essential data
2. Mental status examination—24 questions
3. Standardized progress note
   a) aide's report
   b) evaluator's observation
   c) evaluator's opinion of status

The front sheet of this form includes such essential data as age, sex, diagnosis, previous treatment, and a brief history. In addition, the following items listed in Table 3 are included:

1) Brief history and essential data.
2) A mental status examination. (This is composed of 24 questions; the patient's answers to these questions are recorded verbatim.)
3) A standardized progress note which includes:
   a) The aide's report
   b) Observations by the evaluator (including blood pressure and weight)
   c) Space for the opinion of the observer as to the patient's status

The aide's report includes the following: patient's activities on and off the ward; whether these activities are carried out with or without persuasion; whether the patient socializes; interest in personal appearance; and a sleep record. In addition, behavior on the ward: whether patient was incontinent, assaultive, etc. There are 21 items in this group.

The interviewer then observes the patient to determine the following: personal appearance, eating habits, facial expression, gait, affect, social confidence, attention speech and orientation. Finally there is space provided for the observer to write a progress note describing his impression of any change that has occurred during the week.

This form is completed before the study is initiated, at three week intervals and at the termination of the project. In addition, the standardized progress notes are recorded each week.

This particular method of recording behavioral change is not presumed to be the answer to the problem of evaluation. However, it does have these advantages: the form has been altered on four occasions and questions which either failed to produce a response or which gave data which did not appear to be significant were dropped. Also, it fits the situation in which it is used.

Criteria of Improvement

Table 4 shows the items which are taken as indicative of minimal improvement; there must be a consistent though slight increase in two or more of the following as compared to the control evaluation:

TABLE 4

Criteria of Improvement

Increase in:
- Participation in activities
- Socialization
- Interest in personal appearance
- Appropriate affect and speech
- Attention span, alertness
- "Feeling better" (patient's statement)
- Friendliness
- Cooperation
- Attempt to communicate

Decrease in:
- Agitation
- Tension
- Incontinence
- Overt hostility

Results

Of the 26 patients treated, three showed consistent improvement and a fourth patient showed a desirable change which, however, was not maintained. One of the three patients that improved became less agitated, showed more appropriate affect and increased interest in his surroundings. Prior to treatment, this patient was hostile, agitated and walked about swinging his hands over his head. He had been hospitalized two years when he was forty years of age and was diagnosed schizophrenic reaction, schizoaffective type. He had previously received chlorpromazine and reserpine with little change in his behavior.

The second patient who improved was friendlier, more alert and showed an increased interest in his surroundings and participated in some activities. Prior to treatment he had been quiet, showed little initiative and would seclude himself under the

steps of the laundry where he worked. This patient had been hospitalized 22 years. He had not responded to three previous efforts with phenothiazine medication. He was diagnosed schizophrenic reaction, simple type. He is 57 years of age.

The third patient stated he felt better, initiated conversation and was neater in appearance. During the control interview, he was restless and gave little evidence of interest in himself or his surroundings. This patient is 54 years of age and had been hospitalized 29 years. He is diagnosed schizophrenic reaction, simple type. Treatments previously tried included hydrotherapy in 1934, insulin in 1938, and four research preparations.

The only side effects which could be attributed to the medication occurred in two hypertensive patients. The first patient had a control blood pressure of 190/120. At the end of the first week, the blood pressure was 218/120 and at the end of the second week it was 230/138. The medication was discontinued and a week later it was 208/130. The second patient had a control reading of 210/118 and at the end of a week's treatment, it was 218/132. The drug was terminated. No evidence of liver toxicity or hypotension was noted.

Another patient, who responded slowly, if at all, to questions during the control interview, who had been inappropriate in her speech and showed little affect, became "brighter" and less agitated on 50 mgm. daily. However, as the dose was raised she showed an increasing agitation with constant "chewing" movements and much swinging of her arms. The medication was discontinued after she received 150 mgm. daily during the 5th week.

The remaining 19 patients showed no appreciable change during the six weeks of the study. The chronicity of the group treated and their previously refractory state anticipates these results. The lack of side effects, except in the two hypertensive patients, was notable.

Clinical Evaluation of Nialamide in Hospitalized and Non-Hospitalized Patients

JAMES A. JOHNSON, JR., M.D.

The following is my experience with nialamide in 33 hospitalized and non-hospitalized patients during the past four months. The hospitalized patients were recent admissions to the white male reception service of the State Hospital and were under my direct supervision and were seen daily. Two interviews weekly of 15 to 30 minutes with each patient were held for evaluation and psychotherapy. The nurse and attendants carefully observed the patients for side effects. A placebo only was used in five cases. The patients were told they were being given a new medication that might be helpful.

The non-hospitalized patients were observed by the author's father, a general practitioner in a small city of 4,000 people in the western part of Georgia. Patients were evaluated once weekly.

Nialamide was given in several dosage scales from 10 mgs. t.i.d. to 25 mgms. q.i.d. Examination of blood pressure, pulse, respiration, and weight were done weekly. Complete blood counts and urinalyses were done at frequent intervals. The thymol turbidity test was done on all patients at varying intervals of two to three weeks.

Nialamide was given to a variety of patients with depression including those whose illnesses were due to alcoholism, depressions, and schizophrenic reactions. Eight patients were suffering from depression of varying degrees; seven had symptoms that would usually have required the consideration of electric shock treatments; four were agitated. The ages varied from 30-64 years. Nialamide was given in doses of 30 to 100 mgms. per day; the usual dose ranging from 75-100 mgms. per day. Clinical response was noted in some cases as early as the third day and by seven to 10 days as a general rule. Five patients were discharged from the hospital after an average stay of 30 days (14-40 days). Follow-up at this date indicates satisfactory adjustments. One patient with a history of two previous depressions in the past 10 years, was admitted with a severe, agitated depression. He did not respond to nialamide in dosage of 100 mgms. per day for 14 days. The patient was then given ECT with a satisfactory response.

The following cases are descriptive of the treatment in this series of depressions:

(1) A 47-year-old male was severely depressed with weight loss, insomnia, anorexia, extreme guilt feelings, and actively suicidal. This was his first mental illness. He had been a successful farmer. His wife had died six months before from a lingering malignancy of three years' duration. Two months after the wife's death, his 15-year-old daughter became pregnant out of wedlock. For several months his depression was manifested by headaches, stomach distress, and generalized malaise. One month before admission he became even more depressed. His admission to the hospital was precipitated by a suicide attempt. He was given 25 mgm. of nialamide twice a day for 21 days. Soon he was able to talk about the loss of his wife and the daughter's pregnancy. Attempts were made to understand the daughter's behavior as a result of her own grief over her mother's death. Arrangements were made for her to stay in another community. The patient improved quickly. Within 10 days he was more alert and pleasant and slept better. At the end of 14 days he asked for work on the ward. He began to talk about farming and contacted his sons to discuss producing a crop this year. He was discharged from the hospital five weeks after admission. A follow-up four weeks later revealed that he was feeling fine and was actively farming again.

(2) A 53-year-old male truck driver came into the hospital with a depression of nine months' duration. Numerous aches and pains had led him to a number of doctors and hospitals where repeated laboratory and x-ray examinations were negative. Two months before admission lassitude, anoraxia, insomnia, and fatigue became more pronounced. His primary concern seemed to be memory impairment, difficulty in concentration, and confusion in relation to his work. On admission he was moderately depressed but in good contact with his surroundings. He was given nialamide 25 mgms. t.i.d. for 12 days. Within three days there was a noticeable improvement. At the end of two weeks he was on the way to recovery. When the drug was stopped, he became somewhat concerned for several days; however, this did not interfere materially with his improvement. He was discharged from the hospital in one month. His memory and power of concen-

tration were better but he was dubious of trying to work again. One month later he telephoned to report happily that he had been back at work two weeks. He described his memory as being fine and his mood excellent. He had gained over 10 pounds and was sleeping soundly.

Nialamide in doses of 50-100 mgs per day was given to eight patients 20-44 years of age with diagnoses of schizophrenic reaction and improvement was noted in four cases. Three of these received 20 mgs nialamide every six hours for 72-86 hrs. by intramuscular injection. One patient was a disturbed, hostile, assaultive, hallucinatory catatonic who had to be secluded on admission. Within 48 hours after receiving the drug he was out of seclusion and was cooperative, pleasant and manageable. Another chronic schizophrenic with several prior admissions dating to 1953, came into the hospital in a panic state with confusion, hallucinations, excitement and destructive behavior. Within 72 hours there was a marked change in his behavior and attitude. The third patient, who had a five year history of mental illness, was depressed, paranoid, evasive, and bizarre on admission. Within 72 hours he had a more pleasant mood, a cooperative attitude, etc., even though he continued to be quite sick. The fourth patient was considered to be a paranoid schizophrenic with a large element of depression. He received nialamide 50 mgms. per day for 35 days. The depression lifted after six weeks and he was allowed to go home on furlough. He is making a marginal adjustment.

Four patients in this group did not respond to nialamide. They were clear cut chronic schizophrenics; paranoid (2), simple (1), catatonic (1). Two of these four patients received t hedrug for as long as 42 days with no change in their status. The catatonic patient remained agitated and destructive. He did not respond to Nialamide, Sparine, or Thorazine but did improve on ECT.

There were two schizophrenics who received the placebo. Both patients presented some interesting features. One was a 30-year-old male with a history of a marginal adjustment for the past seven years including an eight weeks hospitalization in 1955 at another institution. The present illness was precipitated by family difficulties and was manifested by aggressive feelings (i.e., wanting to hurt people) associated with a depressive element because of the fact that these aggressive feelings were present. He spoke of feeling "worthless" and "no good." Insomnia, anorexia, and weight loss were present. He improve quickly and felt that the medicine was wonderful. He continually spoke of how nice the personnel were, how often he was talked with, and how appreciative he was of this attention. He was discharged within 30 days. Reports on his progress show a good adjustment at this date.

The other patient who received the placebo was a paranoid schizophrenia with a poor adjustment for a number of years. He received a placebo for 11 days. His fantasies regarding the drugs were: (1) that it would kill him, (2) that he "would go out of this world," and (3) that the medicine would make him stiff.

Seven patients with problems associated with alcoholism received nialamide. Three patients with similar problems received a placebo. The hospital course was similar in both groups. Alcoholics usually stay at the hospital a minimum of 30 days. Once they are over the acute episode, they are willing and cooperative patients—regardless of medication. Follow-up studies on the seven patients are incomplete and inconclusive. Two alcoholic patients who received nialamide in the hospital are being seen twice monthly and are over 60 days without alcohol. Statements of several patients who took the placebo are worthy of note. "I feel that the medicine helped." "It made me drowsy after I took it." 'It must be good medicine." "I felt more nervous when the medicine was stopped." One 50-year-old male felt that he was sexually stronger as nocturnal emissions occurred for the first time in several years.

Five non-hospitalized patients have been treated with nialamide in the past 2½ months. Two of these are depressions. The first was a successful attorney, handicapped physically by poliomyelitis of 20 years' duration. He had been depressed for six months. Marital problems were felt to be playing a major part in his illness. He re' ceived nialamide for four weeks in dosages

up to 100 mgms. per day. He did not improve and was referred to a private psychiatrist for additional treatment. The second was a 63-year-old farmer who gave a history of depression for two years. The initial illness occurred after surgery for a ruptured intervertebral disc in January 1957. ECT was given in 1957 and 1958 with only temporary improvement. Nialamide was prescribed initially 25 mgm. twice a day and later increased to 25 mgms. four times a day. He continues on treatment and is considered to be only slightly improved at this time.

Toxic effects from nialamide were not encountered. No blood dyscrasias or significant changes in the blood picture were observed. All liver function tests were normal. Several patients had transient traces of albumen in urine samples; however, these were thought to be laboratory errors. There were no deviations in the blood pressure. Three patients who had been on nialamide over 14 days developed bradycardia. The pulse rate in all varied between 60 and 66 per minute. Electrocardiograms reported normal tracings, bradycardia. After the drug was discontinued the pulse rate increased approximately 10 to 15 beats per minute. Edema of the lower extremities was not seen. Dermatitis or other skin disturbances were not present. Gastrointestinal symptoms did not occur. A chronic alcoholic who received 100 mgm. per day for 27 days complained of sluggishness and drowsiness that cleared up in three to four days after the drug was stopped. This sluggish, drowsy reaction was noted by the psychologist when testing the patient. Later studies repeated by the psychologist indicate that the patient was alert and responsive with no sluggishness present.

Patients receiving nialamide by intramuscular injection did not show any toxicity or side effects. Blood pressure, pulse, respiration, and weight were taken daily. No skin or muscle irritation at the site of the injection was present.

Three patients were given ECT three days after discontinuing nialamide. No untoward effects in the convulsive pattern and recovery period were observed.

In the curative process, besides the drug, other factors must be considered. The meaning and feeling transmitted to the patient by the doctor and other personnel are important. The personality of the doctor, the suggestibility, and the intent of the relationship with the patient are factors of great importance. Similarly, the attitude and motivations of the nurse and attendants play a significant part. The patients in this study knew that something new was being tried that it was suggested it had an encouraging atmosphere and that it might be helpful. They received extra consideration and observation as more attention was paid to their physical status, to blood pressure examinations, weight, questions about their eating and sleeping habits, side effects from the medicine, etc. They went to the laboratory more frequently for different tests. The attendants were more observant and watched closely for any unusual happenings. Undoubtedly these factors are an integral part of the curative process

Clinical Experiences with Nialamide in Depression

RICHARD C. PROCTOR, M.D.

Happiness and joy and the contrasting states of grief and sorrow are affective disturbances which every normal person experiences to some degree. It is only when such states are out of keeping with the individual's actual circumstances and surroundings that they become pathological or morbid.

Depressions were first described by Aretaeus of Cappadocia between 200 and 300 A.D. He clinically outlined melancholia and attributed it to a disturbance of "black bile." "If it (black bile) be determined upwards to the stomach and diaphragm, it forms melancholy, for it produces flatulent aructations of a fetid and fissured nature and it sends rumbling wind downward and disturbs the understanding." Pathological mood swings are mentioned in the writings of Hippocrates, Pluto, Galen, Alexander of Tralles and others. The Bible records the melancholies of Job and King Saul.

Shakespeare in *Macbeth* records the seeking for relief of depressive states when Macbeth asks the physician,

> "Canst thou not minister to a mind diseased,
> Pluck from the memory rooted sorrow,
> Raze out the written troubles of the brain
> And with some sweet oblivious antidote
> Cleanse the stuff'd bosom
> Of that careless stuff
> Which weighs upon the heart?"

There is a constant need for new methods in the treatment of all human ills. Depressive reactions are common to the practice of medicine. There were 25,000 known suicides last year in the United States, a total of fatalities greater than from all infectious diseases combined. Many more probably occurred, but were not officially known or reported.

For many years, electroconvulsive therapy has been the treatment of choice for depressions. We have recognized, however, the physical and psychological limitations of this type of therapy. A. C. Washburne reported in the Annals of Internal Medicine in February 1950 on the use of large doses of nicotinic acid in the treatment of depressive reactions. This was followed later by a report by this author in the North Carolina Medical Journal in September 1953. Recently, in the treatment of depressed psychotic patients, Marsilid has had some clinical success. Its shortcomings have indicated a need for new agents with similar therapeutic effects, but with lower toxicity. This presentation is a report of the clinical use of nialamide, one of these newer agents. This study was carried out at the Bowman Gray School of Medicine of Wake Forest College, and in the clinics and wards of the North Carolina Baptist Hospital. No attempt will be made to cover the basic pharmacology or animal toxicity studies in this paper, but rather I will attempt to present the results in a group of patients seen in therapy and who were suffering from various depressive reactions.

A total of 57 patients have been treated since the study was initiated in January 1958. Seven of the 57 were eliminated because of insufficient follow-up. The remaining 50 were divided as follows: 34 females and 16 males; below the age of 20, 1 female; aged 20-29, 4 females and 2 males; aged 30-39, 8 females and 1 male; aged 40-49, 8 females and 7 males; aged 50-59, 10 females and 4 males; aged 60-69, 3 females and 2 males; above the age of 70, no patients.

The overall symptomatic improvement rate in the total group of 50 patients was as follows: improved—28, 9 males and 19 females; unimproved—22, 5 males and 17 females. In breaking these figures down further some very interesting things are noted, and perhaps some early postulations can be made. In the below 20 age group there is only 1 patient, female, and she showed improvement. In the 20-29 age group, 4 out of 4 females improved and 1 out of 2 males. In the 30-39 group, 5 out of 8 females improved and 1 out of 1 male improved. In the 40-49 group, 5 out of 8 females and 5 out of 7 males improved. In the 50-59 group, only 2 out of 10 females improved and 2 out of 2 males improved. In the 60-69 age group, 1

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out of 3 females and 2 out of 2 males showed clinical improvement of a significant nature.

The difficulty in analyzing figures and statistics is well recognized. One can rely only on one's clinical judgment and intellectual honesty in seeking answers to the presenting situations and problems. It seems from preliminary studies that nialamide is more effective in male and female patients under the age of 50, where the symptom of depression is dominant. Above 50, it is less effective in women than in men.

The breakdown of patients diagnostically was as significant as the breakdown previously covered. Patients diagnosed as having "neurotic depressions" showed nine out of 12 females improved and seven out of nine males improved. Patients with psychotic-depressive reactions showed only six out of 17 females improved and two out of three males. Patients with recurrent depressions of the manic-depressive type showed three out of five females and two out of four males with improvement. I feel that these are significant in that the patients with neurotic-depressive reactions tend to be younger than those with psychotic-depressive reactions, and they showed a better response to nialamide therapy. This raises the question of age, or perhaps an endocrine factor that may play a part in the causative mechanism of psychotic-depressive reactions in the group over the age of 50.

Another question raised in reporting the response and the clinical effects of new drugs is that of side effects. In the 50 patients of this group there were no significant changes found in the routine hemograms or urograms. The only side effects noted were as follows: One patient develcped dizziness and feelings of faintness, was found to have developed a drop of 30 points in systolic blood pressure. She was taking only 10 mgm. three times per day, and the symptoms showed up after one day. She was taking no other medication at the time. The drug was discontinued, and the blood pressure promptly rose to its previous level of 130/80. One patient developed nausea and vomiting three days after starting treatment which continued for ten days until the medication was discontinued when the nausea and vomiting ceased within 48 hours. Unfortunately, this patient would not agree to resume the medication. One patient thought the medication kept him awake at night, but not enough to require any bedtime sedation. These were the only side effects encountered in our 50 patients.

Dosage was routinely 25 mgm. three times a day. A few patients were increased to 25 mgm. four times a day but there was no significant change in their response on the increased dosage. In five patients who showed improvement medication was reduced after 6-8 weeks to 10 mgm. three or four times a day with maintenance of the improvement.

The response of two patients is considered worthy of separate reporting. One was a 48-year-old, married white female with a history of four previous depressions during the past fifteen years each requiring hospitalization and electroconvulsive therapy. During three of these previous depressive reactions she had been treated by the author. She had responded on each occasion after 8-10 electric treatments and remained symptom-free until the appearance of the next depression. She showed with each depression a typical picture of agitation, restlessness, crying, insomnia, anorexia and weight loss. Her symptoms were worst in the morning. In addition she showed ideas of reference and persecution, feeling that her neighbors were talking about her, that her husband did not understand her and was trying to get rid of her. She was seen on March 28, 1959 with the same symptoms as in her previous depressive illnesses and she was started on nialamide, 25 mgm. three times a day. By April 18 there was a complete change in the clinical picture. She was cheerful and her affect was normally labile. There was no evidence of ideas of reference, she was eating and sleeping well. She was seen again on May 9 and had continued to maintain her improvement on her lower dosage.

Another patient was a 48-year-old, married white male who was seen on February 13, 1959 with depression, agitation, restlessness, insomnia and anorexia. He felt that he was a failure at h.s job and that he should not continue at it. He was general superintendent of a successful furniture manufacturing plant and had been in this type of work for twenty years. He had lost consid-

erable weight, brooded over the business and was unable to make decisions. He was started on nialamide 25 mgm. three times a day. After two weeks he reported some improvement in his symptoms but it was not marked. The dosage of nialamide was increased to 25 mgm. four times per day (at bedtime being added). One month later he showed marked improvement. He was cheerful, eating and sleeping well, was no longer agitated, was able to make decisions, and able to do his job. The dosage was reduced to 10 mgm. three times a day and at bedtime, and he was re-examined five weeks later. At the last visit he had continued to maintain his improvement as previously mentioned, and the dosage was further reduced to 10 mgm. three times a day.

What conclusions can be drawn from this series of 50 cases? First, nialamide seems to offer considerable promise in the treatment of certain depressive reactions. It seems most useful in the treatment of neurotic-depressive reactions in patients under 50, and it is of benefit in some patients with depressions of the manic-depressive type. In the older patients suffering from depression, it seems more useful in males than in females. I am unable to explain these differences clinically. Nialamide is remarkably non-toxic as side effects are very few and minimal. Certainly nialamide seems to be a useful addition to the psycho-pharmacologic armamentarium.

Discussion

TRAJAN SHIPLEY, M.D.

At this point in the afternoon's program I feel that congratulations are in order. I'd like to congratulate the speakers whose papers I am to discuss, Doctors Smith, Proctor, and Johnson. First, I recall my pharmacology professor, Clinton Thienes, saying, "Be not the first to use a new drug, nor the last." He did not go ahead to say who was to be the first to use the new drug; today we have seen many pioneers. I feel that they all deserve congratulations, all the participants, for it is indeed a big step between animal experimentation and human usage.

The results have shown nialamide to be effective in psychoneurotic conditions and some instances of psychosis, either of brief duration or long standing. The results of Doctors Smith, Proctor and Johnson have verified this. None of these papers used double blind techniques. I'd like to say a word in this regard. There are some who might use this as criticism of the work which has been accomplished. Fashions in medical treatment change. I'd like to mention, too, that there has been a fashion change in the double blind technique. If I can call on your memory, years ago in England, when Foxglove or digitalis was discovered, the shoe was on the other foot. The old witch had something—what the devil is it? It was known to be effective. Today, we are given the stuff—what will it do? The oldest method of evaluating a drug has been the eyes open, blinders off, glasses on, visibility clear method. And I'd like to put in a word in favor of this method. Most of the papers today have used this method. After all, we can evaluate our patients' reactions and this is the most worthwhile method. However, there is no question about the usefulness of the double blind method and its accuracy.

There has been a wide dosage range mentioned, and this has been borne out in more than one paper. Dr. Johnson stopped his dosage at 100 mg. a day in some patients. I would like to tell you some of the things that were apparent only to someone in Georgia who had access to the local newspapers. This, potentially, might occur to anyone doing investigative work with new drugs. At one stage, the Governor suddenly announced that experimentation on patients at Milledgeville would stop; and as Dr. Johnson mentioned, the newspapers carried the story. Such executive action is not without precedent. I recall an incident in Military Service where the Area General became perturbed about the progressive increase of VD in a group of young men who had decided that they had better live while they were alive. He told the surgeon and the commander involved that this increasing incidence should stop. Well, even the bacteriological world seems to take cognizance of such a command because the VD rate precipitously declined. It is noteworthy, however, that the incidence of coryza, dandruff, and ingrowing toenails rose greatly, and this apparently was more tolerable to the general.

Dr. Smith used a six week period in evaluating the effective treatment. I wonder if it might be worth continuing the evaluation longer. As we recall, in the history of the use of reserpine it was found that in some instances a desirable result could be obtained if a longer period were available. Naturally the cases are low in number; more cases are needed, for all aspects of the investigation.

I had the opportunity of administering this medicine to 47 patients. One-third were psychotic and two-thirds were psychoneurotic. You have heard enough statistics this afternoon. There is one case that I would like to point out in this series. This was a case of manic-depressive psychosis, in depression, in a 64 year old woman. She had been placed on a schedule of 100 mg. nialamide daily at her home, a distance of about 250 miles from our office. She failed to keep a follow-up appointment. Subsequently she committed suicide at home. This is one of those unfortunate results of any treatment but a danger which must be kept in mind. I would

like to have been able to provide both the brain and the liver to Dr. Udenfriend for study. I hope the future does not provide another opportunity.

Twelve of the patients were given nialamide in conjunction with ECT. There were no complications, and I can conclude in this small series that neither therapy is a contraindication to the other. There were other drugs which were used without difficulty in conjunction with nialamide including various phenothiazines and barbiturates. In the use of ECT, both Pentothal and succinyl choline were used without incident in nialamide treated patients. I had no opportunity to observe any epinephrine effects.

Closing Remarks

T. R. ROBIE, M.D.

President, Eastern Psychiatric Research Assn.

I see in this audience a number of psychiatrists and other doctors who have been intimately associated with the administration of electroshock therapy since its introduction in this country twenty years ago. Many are members of this association, whose members have played a prominent part in making the administration of electroconvulsive therapy a safer and more effective procedure.

It is my belief that electroshock has played a greater part than is generally realized in the inception of research meetings such as this. The fact that electricity can induce remission from severe and disabling melancholia certainly has suggested to many that a chemical could perform this same mission in a safer manner and with less loss of time and at less cost to the patient. These were boons not contemplated when chemical research first started in this sphere.

I am convinced that there is no advocate of electric shock in the land who wouldn't be overjoyed to see the day when chemical science will have advanced to the point where he would no longer need to push the (electric) button. The psychiatrist administering cerebral electrotherapy knows that the patient undergoing this treatment experiences a degree of anxiety concomitant with that experienced before any surgical operation, in apprehensive expectation before each shock treatment.

Since it has never been proved that this severe additional anxiety is a necessary part of therapeutic effectiveness and because of the many other advantages that can accrue from the chemical approach, I say: "Speed the day when our knowledge makes possible a remission of symptoms of all types of melancholia, by some safe chemical method such as has been discussed here today," and also speed the day when a chemotherapy will be discovered that is efficacious for schizophrenia. And looking still further into the future that lies ahead in biochemistry, speed the day when we will have discovered a simple chemical which can be administered like a vitamin, from childhood on if necessary, that will prevent the formation of those chemicals in the human being that are the cause of these two major mental diseases, which disable more human beings than any other cause.

In his introductory remarks opening the second symposium on Amine Oxidase Inhibitors, Dr. D. Wayne Woolley of the Rockefeller Institute, expressed several concise comments which aptly described the aim of that 1958 symposium. They apply equally well to this meeting and I therefore will abstract them for you, but with full realization that only by reading the full context can one grasp the total import of his comments. He said, in part:

"We will be concerned during this conference with an important group of hormones, serotonin, adrenalin, noradrenalin, acetylcholine and histamine, and more particularly with drugs that cause increased concentration of them in the human body.

"These hormones, formed by enzymic reaction, are stored in certain cells in a pharmacologically inactive form. A destructive enzyme provided in the body can actively destroy serotonin, nor-adrenalin or adrenalin, which are monoamines. By inhibiting this destructive enzyme we can allow accumulative and continuing action of the hormones on the muscles and nerves.

"In 1954 Wooley (D.W.) and Shor brought forth evidence that some mental disorders may arise from a deficiency in the serotonin content of the brain, and suggested that a rational way of treating these disorders would be to compensate for the deficiency by increasing the serotonin content of the brain. Inhibiting the destruction of serotonin by administering amine oxidase inhibitors is one way of accomplishing this."

I know of no one who could put this into words better than Dr. Wooley. Today we are discussing how a new amine oxidase inhibitor accomplishes this aim.

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